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1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8-Triazanaphthalenes

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Benzofuroxans

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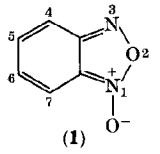
I. Introduction

The benzofuroxan [benzofurazan oxide,* 3,4-benzo-1,2,5-oxadiazole-2-oxide, or 2,1,3-benzoxadiazole-1-oxide (**1**)] ring system has been reviewed briefly on several occasions, notably by Kaufman and Picard,[1] Boyer,[2] and Behr.[3] The most recent of these[3] covers the literature until 1959, and since that date there have been many advances in the subject. This, we feel, justifies the field being covered once more, and its separation from the monocyclic 1,2,5-oxadiazole oxides—the furoxans. We consider also other furoxano-fused compounds in this chapter, subject to the limitation that the ring adjacent to the furoxan is aromatic and six-membered..



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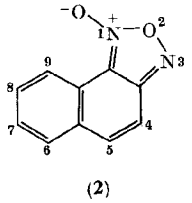

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The benzo-annellated derivative naphtho[1,2-*c*]furoxan is numbered according to the system (**2**)] shown. In the literature the name 1,2-naphthofuroxan may often be found, with the same numbering as for a 1,2-disubstituted naphthalene. Although the latter method is perhaps a little clearer to follow, the more systematic scheme (**2**) will be adhered to in this chapter.

II. Structure

The literature on benzofuroxans is considerably complicated by uncertainties concerning their structure, which were resolved only in 1960. Thus, Beilstein's *Hauptwerk* includes them in Volume 7 (as derivatives of *o*-quinones, depicted as dioxadiazines, and named as

* *Chemical Abstracts* preferred name, which seems to us to embody the disadvantages of both systematic and trivial nomenclature.

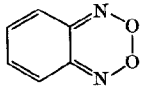
[1] J. V. R. Kaufman and J. P. Picard, *Chem. Rev.* **59**, 429 (1959).

[2] J. H. Boyer, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 7, pp. 462–508, 1961.

[3] L. C. Behr, *in* "Chemistry of Heterocyclic Compounds" (A. Weissberger, ed.), Vol. 17, pp. 295–309, 1962.

o-dinitroso compounds); in the First Supplement they are in Volume 27 (as dioxadiazetidines), and in the Second Supplement also in Volume 27 (this time as oxadiazole oxides).

Since the earlier reviewers, and Mallory and Wood,[4] and, for the earlier literature, Hammick *et al.*[5] have summarized the history of the structure problem fairly fully, and since it cannot in any case be treated properly in isolation from that of the monocyclic furoxans, we shall present only a brief outline here. The earliest formulas to be suggested (**3** and **4**), in connection with 1,2-naphthofuroxan, discovered by Koreff[6] and von Ilinski[7] in 1886, were open to the objections that the first is a peroxide structure, whereas the benzofuroxans



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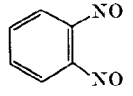

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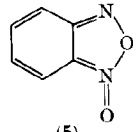

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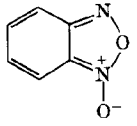

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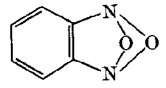


(6)

are only weak oxidizing agents and do not show other properties commonly associated with the peroxy linkage, and the second contains nitroso groups, although the usual chemical and optical properties of *C*-nitroso compounds are lacking. The furoxan structure (**5**), which in its modern form (**1**) is accepted today, was suggested by Green and Rowe in 1912,[8] but abandoned a year later[9] in favor of **6**, because the unsymmetrical structure of **5** required that 4- and 5-substituted compounds should form two isomeric series. However, hypochlorite oxidation (a general method for obtaining benzofuroxans from

[4] F. B. Mallory and C. S. Wood, *Proc. Natl. Acad. Sci. U.S.* **47**, 697 (1961); *Chem. Abstr.* **55**, 23504 (1961).

[5] D. L. Hammick, W. A. M. Edwardes, and E. R. Steiner, *J. Chem. Soc.* p. 3308 (1931).

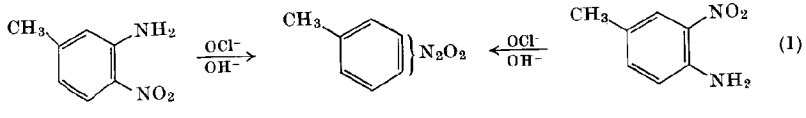
[6] R. Koreff, *Ber. Deut. Chem. Ges.* **19**, 176 (1886).

[7] M. von Ilinski, *Ber. Deut. Chem. Ges.* **19**, 349 (1886).

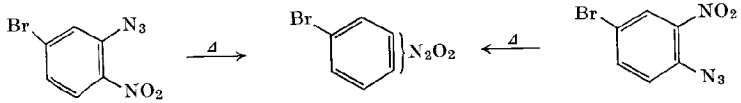
[8] A. G. Green and F. M. Rowe, *J. Chem. Soc.* **101**, 2452 (1912).

[9] A. G. Green and F. M. Rowe, *J. Chem. Soc.* **103**, 897 (1913).

o-nitroanilines, see Section IV) of 3-amino-4-nitrotoluene and 4-amino-3-nitrotoluene led to the same methylbenzofuroxan [Eq. (1)].[9] Almost simultaneously, Forster and Barker[10] obtained the same monobromobenzofuroxan from two isomeric bromonitrophenyl azides [Eq. (2)]. Similar results had also been obtained earlier with naphtho-

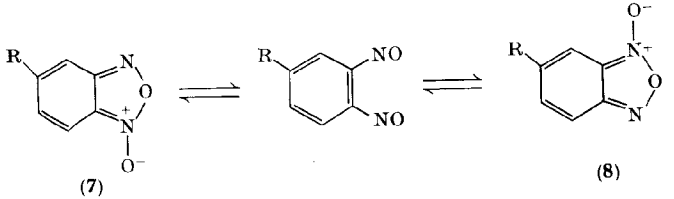


(1)



(2)

[1,2-*c*]furoxan.[11, 11a] The benzofurazan oxide structure **5** (or **1**) was revived by Hammick *et al.* in 1931,[5] who compared the bromination of benzofuroxan and benzofurazan, and also from parachor considerations favored **5** over the structures **3**, **4**, and **6**. They also suggested that a rapid interconversion of unstable into stable isomers, probably via the dinitroso structure [Eq. (3)] could be the reason for the formation of single compounds when pairs of isomers were to be expected.

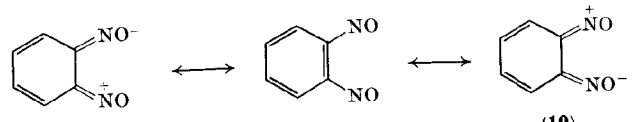


(3)

(7) (8)

In 1955 Boyer *et al.*[12] challenged this formulation, and suggested a static, mesomeric system rather than a dynamic, tautomeric one, with contributing structures of type **9** and **10** to a symmetrical resonance hybrid, proposing the name *ψ*-*o*-dinitrosobenzene for the parent system. This notion, however, raised more problems than it solved,

[10] M. O. Forster and M. F. Barker, *J. Chem. Soc.* **103**, 1918 (1913).
[11] M. O. Forster and H. E. Fierz, *J. Chem. Soc.* **91**, 1942 (1907).
[11a] M. O. Forster and M. F. Barker, *Proc. Chem. Soc.* **29**, 152 (1913).
[12] J. H. Boyer, R. F. Reinisch, M. J. Danzig, G. A. Stoner, and F. Sahhar, *J. Am. Chem. Soc.* **77**, 5688 (1955).



(9) (10)

and shortly afterward it was demonstrated by several groups of workers, practically simultaneously, on the basis of both NMR (Section III, C) and X-ray (Section III, D) evidence, to be incorrect.

The present-day picture of the gross features of the benzofuroxan structure differs slightly from that of Hammick,[5] in that both isomers (e.g., **7** and **8**) of the tautomeric system [Eq. (3)] are known to be present in solutions of most benzofuroxans, although usually only one is detected when there is a 4- but no 7-substituent.[13] Apart from indications from the thermodynamic parameters provided by kinetic measurements,[14] and arguments against **6** as an intermediate, based on the inability of 2,5-disubstituted benzotriazole 1-oxides to rearrange to their 3-oxides,[15] no sound evidence has been obtained for the intermediary *o*-dinitrosobenzene. However, Hammick[5] *et al.* cited the greenish-yellow color of hot solutions of benzofuroxan, which faded on cooling, and using bond energy arguments Mallory and Cammarata[16] showed that other possibilities are far less likely. The thermodynamic constants for the interconversion process were obtained from NMR spectra at variable temperatures, and so will be discussed in Section III, C. In the solid phase, only one isomer of 5-chloro- and 5-bromobenzofuroxan is seen (Section III, D).

The tautomeric structure leads to ambiguities in the nomenclature of compounds in this series. Thus, 5-methyl- and 6-methylbenzofuroxan denote two different molecules which, because of their interconversion, cannot be isolated separately at normal temperatures. Throughout this review, when we intend to refer to the ambiguous mixture, we shall use the system employing the lowest numbers. The above methyl derivative, for example, will be described as 5-methylbenzofuroxan regardless of the form adopted in the crystal. When a

[13] R. K. Harris, A. R. Katritzky, S. Øksne, A. S. Bailey, and W. G. Paterson, *J. Chem. Soc.* p. 197 (1963).
[14] F. B. Mallory, S. L. Manatt, and C. S. Wood, *J. Am. Chem. Soc.* **87**, 5433 (1965).
[15] F. B. Mallory and C. S. Wood, *J. Org. Chem.* **27**, 4109 (1962).
[16] F. B. Mallory and A. Cammarata, *J. Am. Chem. Soc.* **88**, 61 (1966).

particular tautomer is to be designated, this will be done by italicizing the numeral.

Linnett and Rosenberg have discussed the electronic structure of a number of nitroso and potential nitroso systems, including benzofuroxans, using the nonpairing approach.[17]

III. Spectroscopic and Other Physical Properties

A. Infrared Spectra

No systematic investigation into the vibrations of the benzofuroxan molecule has been reported. Infrared data are available for a number of compounds, however. Boyer *et al.*[18] in 1953 listed four bands in the benzofuroxan spectrum: at 1630, 1600, 1545, and 1500 cm^{-1}. It is the present authors' experience that four strong bands of comparable intensities at or near the frequencies quoted commonly occur in the spectra of substituted benzofuroxans, and are very useful for diagnostic purposes. One or more bands may be weak or absent, however; for 2,3-pyridofuroxan (4-azabenzofuroxan) only two bands are reported in this region.[18]

Further benzofuroxan spectra are reported by Gaughran, Picard, and Kaufman,[19] who compare them with benzofurazans, by Boyer *et al.*, who find similarities with furoxans[20] and nitroso compounds,[12, 21] and by others.[22, 23] "Hexanitrosobenzene" was shown by IR and Raman spectroscopy to exist in the benzotrifuroxan structure.[24]

[17] J. W. Linnett and R. M. Rosenberg, *Tetrahedron* **20**, 53 (1964).
[18] J. H. Boyer, D. I. McCane, W. J. McCarville, and A. T. Tweedie, *J. Am. Chem. Soc.* **75**, 5298 (1953).
[19] R. J. Gaughran, J. P. Picard, and J. V. R. Kaufman, *J. Am. Chem. Soc.* **76**, 2233 (1954).
[20] N. E. Boyer, G. M. Czerniak, H. S. Gutowsky, and H. R. Snyder, *J. Am. Chem. Soc.* **77**, 4238 (1955).
[21] J. H. Boyer, U. Toggweiler, and G. A. Stoner, *J. Am. Chem. Soc.* **79**, 1748 (1957).
[22] A. S. Bailey and J. R. Case, *Proc. Chem. Soc.* p. 176 (1957); A. S. Bailey and J. R. Case, *Tetrahedron* **3**, 113 (1958).
[23] A. V. Eltsov and L. S. Efros, *Zh. Obshch. Khim.* **31**, 3994 (1961); *Chem. Abstr.* **57**, 8560 (1962).
[24] N. Bacon, A. J. Boulton, and A. R. Katritzky, *Trans. Faraday Soc.* **63**, 833 (1967).

B. Ultraviolet Spectra

Electronic spectral considerations were invoked by Boyer *et al.*[21] in favor of the "ψ-*o*-dinitroso-" structure and by Mallory and Wood[4] against an oxaziridine formulation for the *N*-oxide structure. The spectra of some nitrobenzofuroxans have been reported.[22, 25, 26]

In general, two low-energy band systems appear, which in benzofuroxan itself are strongly overlapping. In substituted compounds,

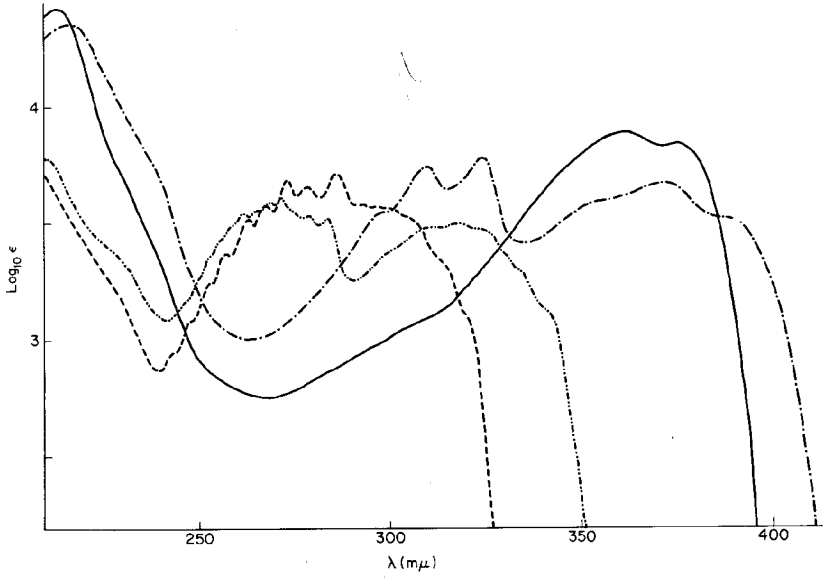


FIG. 1. The ultraviolet spectra of benzofuroxans and benzofurazans in cyclohexane. ————, Benzofuroxan; —·—·—·—, 5-methoxybenzofuroxan; – – – – –, benzofurazan; ···—···—···, 5-methoxybenzofurazan.

for example, the 5-methoxy derivative, the systems become more or less separated, when a higher frequency band with considerable fine structure and a lower frequency band with less well-defined structure can be distinguished. This pattern is very similar to that shown by

[25] A. J. Boulton and A. R. Katritzky, *Proc. Chem. Soc.* p. 257 (1962); A. J. Boulton and A. R. Katritzky, *Rev. Chim. Acad. Rep. Populaire Roumaine* **7**, 691 (1962).
[26] W. P. Norris and J. Osmundsen, *J. Org. Chem.* **30**, 2407 (1965).

benzofurazan, emphasizing the similarity in structure between the two groups of compounds (see Fig. 1). With the strongly electron-donating dimethylamino substituent, the lowest energy band extends well into the visible region of the spectrum.[27]

C. Nuclear Magnetic Resonance Spectra

The first evidence for an unsymmetrical structure for the benzofuroxan molecule and for the tautomerism of Eq. (3) was provided in 1961 by several groups of workers,[4, 13, 28–31] using proton resonance

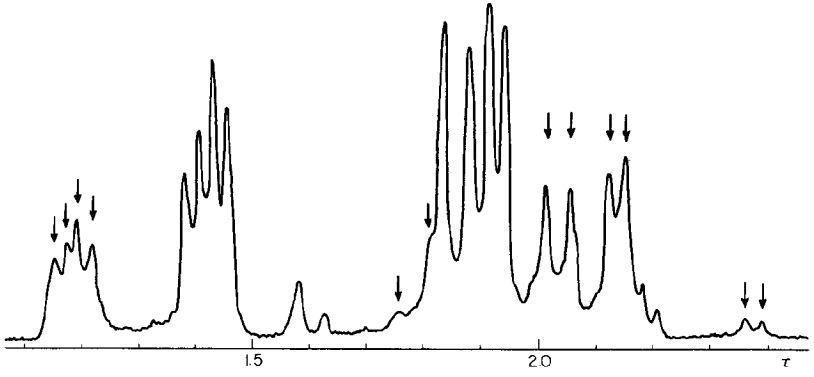
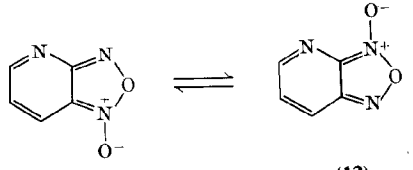


Fig. 2. The proton magnetic resonance spectrum of 5-nitrobenzofuroxan, in acetone at −31°C. The bands marked by arrows arise from the 5-nitro tautomer.

spectra. At low temperatures (−40°) an unsymmetrical (ABCD) spectrum is found, which becomes progressively more blurred with increasing temperature until about 10°, when it begins to gather into a symmetrical form and sharpen, eventually giving a well-resolved symmetrical (A_2B_2) spectrum above 100°. An estimate for the activation energy ΔG^* for the tautomerism of 15 ± 1 kcal/mole was

[27] A. J. Boulton, P. B. Ghosh, and A. R. Katritzky, *J. Chem. Soc.* C, 971 (1966).
[28] R. K. Harris, A. R. Katritzky, and S. Øksne, *Chem. Ind. (London)* p. 990 (1961).
[29] G. Englert, *Z. Naturforsch.* **16b**, 413 (1961).
[30] B. Dischler and G. Englert, *Z. Naturforsch.* **16a**, 1180 (1961).
[31] G. Englert, *Z. Anal. Chem.* **181**, 447 (1961).

made.[13] Similar results for 4,7-dibromobenzofuroxan and 5-methylbenzofuroxan have been reported by Englert,[29, 32] who provides a review of the NMR spectra of benzofuroxans up to mid-1961. Other compounds whose spectra have been analyzed at various temperatures include 5-chloro-,[33] 5-methoxy-,[33] 4- and 5-nitro-,[13] 4,6-[13] and 5,6-[13] dinitro-, 5-methyl-6-nitro-,[33] 5-ethoxycarbonyl,[33] 5-carboxy,[33] 5-acetamido-,[33] 5,6- and 4,7-dichloro-,[14] and 4,7-dibromobenzofuroxans.[14, 29, 32] 5-Nitrobenzofuroxan, to take a typical example, at −31° shows spectra for the two distinct species present in solution; assignment of each spectrum to its tautomeric species was made on the basis of the chemical shifts of the protons, and it was thereby shown that the *6*-nitro structure predominates to the extent of about 70% in the mixture of *5*- and *6*-nitro structures at that temperature (see Fig. 2). 4-Nitrobenzofuroxan shows no trace of the *7*-nitro compound at low temperatures (it would seem unlikely that the compound exists *exclusively* as the *7*-nitro isomer—an alternative possible explanation of the spectra).[13] Pyrido[2,3-*c*]furoxan is nearly all in the *4*-aza structure (**11**) with only ca. 7% *7*-aza (**12**) at −50°.[34]



(**11**) (**12**)

Some workers in this field have used Eyring's equation, relating first-order reaction rates to the activation energy ΔG^*, whereas others have used the Arrhenius parameter E_A. The results obtained are quite consistent with each other (cf. ref. 33); in all the substituted compounds listed above, ΔG^* is about 14 kcal/mole (for the 4,7-dibromo compound an E_A value of 6 ± 2 kcal/mole has been reported,[29] but this appears to be erroneous[14]). A correlation of E_A values with size of substituents in the 4- and 7-positions has been suggested.[14] ΔS^* values (derived from the Arrhenius preexponential factor) are

[32] G. Englert, *Z. Elektrochem.* **65**, 854 (1961).
[33] A. J. Boulton, A. R. Katritzky, M. J. Sewell, and B. Wallis, *J. Chem. Soc.* **B**, 914 (1967).
[34] A. C. Gripper Gray, Ph.D. Thesis, University of East Anglia, 1966.

E. Physical Properties

Benzofuroxan is a very pale yellow crystalline solid, of melting point 72°. Its dipole moment is given by Tappi as 5.29 D, and the moments of eight other benzofuroxans, their molar refractivities, and melting points, are also recorded.[47] It is appreciably steam-volatile, but far less so than its deoxygenated analog benzofurazan. Melting points of benzofuroxans are listed by Kaufman and Picard,[1] and in Section X of this article.

The physical properties associated with the parachor, *viz.*, the liquid surface tension and the density at various temperatures, for benzofuroxan and 5-methylbenzofuroxan are given by Hammick *et al.*[5] The parachor values were reevaluated by Boyer *et al.*[18]

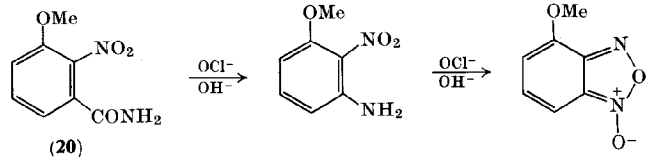
IV. Preparation of Benzofuroxans

Benzofuroxan may be obtained by oxidation of *o*-quinone dioxime.[48] The first benzofuroxan derivative, 1,2-naphthofuroxan, was obtained by this method.[6,7] Suitable oxidizing agents include alkaline ferricyanide,[6,7,48] bromine water,[7] chlorine,[49] and nitric acid.[48–50] The method is of practical value only when the *o*-quinone or its monooxime (*o*-nitrosophenol) is readily available, and since this is not generally the case, other routes, e.g., the oxidation of *o*-nitroanilines[51] and the thermal decomposition of *o*-nitrophenyl azides,[52] are more commonly used.

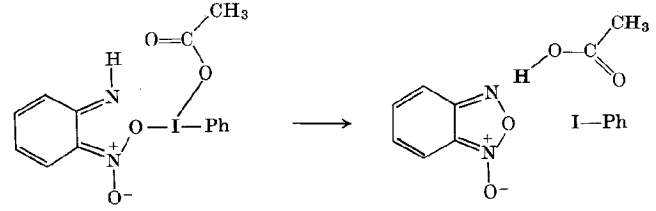
The oxidation of *o*-nitroanilines to benzofuroxans was discovered by Green and Rowe,[8,53] who used alkaline hypochlorite. Although this method has been used extensively,[19,23,54–57] it occasionally fails to

[47] M. Milone and G. Tappi, *Atti 10th Congr. Intern. Chim., Rome*, **2**, 352 (1939); G. Tappi, *Gazz. Chim. Ital.* **71**, 111 (1941).
[48] T. Zincke and P. Schwarz, *Ann. Chem.* **307**, 28 (1899).
[49] J. H. Boyer and G. Mamikunian, *J. Org. Chem.* **23**, 1807 (1958).
[50] S. V. Bogdanov and B. I. Karavaev, *Zh. Obshch. Khim.* **23**, 1757 (1953); *Chem. Abstr.* **48**, 13657 (1954).
[51] F. B. Mallory, *Org. Syn.* **37**, 1 (1957).
[52] P. A. S. Smith and J. H. Boyer, *Org. Syn.* **31**, 14 (1951).
[53] A. G. Green and F. M. Rowe, *J. Chem. Soc.* **101**, 2443 (1912).
[54] F. M. Rowe and J. S. H. Davies, *J. Chem. Soc.* **117**, 1344 (1920).
[55] F. M. Rowe, S. H. Bannister, and R. C. Storey, *J. Soc. Chem. Ind.* (*London*) **50**, 79 (1931); *Chem. Abstr.* **25**, 2424 (1931).
[56] A. G. Green and F. M. Rowe, *J. Chem. Soc.* **103**, 2023 (1913).
[57] G. Tappi and P. V. Forni, *Ann. Chim. Appl.* **39**, 338 (1949); *Chem. Abstr.* **46**, 2540 (1952).

give the expected product. On reaction of aqueous methanolic sodium hypochlorite with 2,4-dinitroaniline, for example, the product is 5-chloro-4-methoxybenzofuroxan, rather than the 5-nitro compound[38] (see Section VII, B). No benzofuroxan was obtained from 2-nitro-*p*-phenylenediamine,[56] 4-amino-3-nitroacetanilide,[56] or 4-amino-3-nitrophenol[58] by this method. Naphtho[1,2-*c*]furoxan was prepared from both 1-nitro-2-naphthylamine and 2-nitro-1-naphthylamine.[59] Hofmann degradation followed by oxidation of the amide (**20**) with sodium hypochlorite and alkali led to 4-methoxybenzofuroxan; alkaline *t*-butyl hypochlorite also gave a small amount of the



(**20**)



(**21**)

same product.[60] Phenyliodosodiacetate in benzene has also been used to oxidize *o*-nitroanilines to benzofuroxans[60–64]; however, the yields vary considerably with the position and nature of the substituents in the benzene ring. With 4- and 5-substituted 2-nitroanilines yields are generally high,[61,63,64] but 3- and 6-substituted compounds give yields varying from nil (6-methyl-) to 93% (3-nitro-).[60] Decomposition of the intermediate (**21**) was proposed as part of the mechanism. Lead tetraacetate oxidation gave no benzofuroxan.[60]

[58] A. G. Green and F. M. Rowe, *J. Chem. Soc.* **113**, 67 (1918).
[59] A. G. Green and F. M. Rowe, *J. Chem. Soc.* **111**, 612 (1917).
[60] L. K. Dyall and K. H. Pausacker, *Australian J. Chem.* **11**, 491 (1958).
[61] K. H. Pausacker, *J. Chem. Soc.* p. 1989 (1953).
[62] G. B. Barlin, K. H. Pausacker, and N. V. Riggs, *J. Chem. Soc.* p. 3122 (1954).
[63] K. H. Pausacker and J. G. Scroggie, *J. Chem. Soc.* p. 4499 (1954).
[64] K. H. Pausacker and J. G. Scroggie, *Australian J. Chem.* **11**, 485 (1958).

The most reliable method of preparing benzofuroxans is by decomposition of *o*-nitrophenyl azides. Decomposition can be achieved by irradiation,[65] or more usually by pyrolysis[22,48,65–67]; temperatures between 100° and 150° are commonly used. Refluxing in glacial acetic acid is the recommended procedure for 4- or 5-substituted 2-nitrophenyl azides, but with 3- or 6-substituted compounds higher boiling solvents are usually necessary. Quantitative studies on the reaction rate have been made,[68–71] and a cyclic transition state invoked,[68,71] an argument which has been used to account for the greater difficulty of decomposition of the 6-substituted 2-nitrophenyl azides.[36] Substituent effects on the reaction rate have also been correlated with Hammett σ constants.[70]

The action of hydroxylamine and sodium acetate in ethanol upon picryl chloride was stated to give 4,6-dinitrobenzofuroxan,[72] and probably some of this compound was formed, although it was later shown[73] that much of the original work was faulty. A report that hydroxylamine and 2,4,5-trinitrotoluene give 5-methyl-6-nitrobenzofuroxan[74] has been found to be incorrect.[75] Benzofuroxan has not been prepared by *N*-oxidation of benzofurazan, and it seems unlikely that this could be achieved, since benzofuroxan itself is oxidizable by powerful reagents to *o*-dinitrobenzene (Section VI,B). A report[76] of the oxidation by nitric acid of anthraceno[1,2-*c*]furazan to the furoxan is incorrectly abstracted.[76a]

[65] P. A. S. Smith and B. B. Brown, *J. Am. Chem. Soc.* **73**, 2435 (1951).
[66] E. Noelting and A. Kohn, *Chem. Ztg.* **18**, 1095 (1894).
[67] E. Schrader, *Ber. Deut. Chem. Ges.* **50**, 777 (1917).
[68] T. F. Fagley, J. R. Sutter, and R. L. Oglukian, *J. Am. Chem. Soc.* **78**, 5567 (1956).
[69] E. A. Birkhimer, B. Norup, and T. A. Bak, *Acta Chem. Scand.* **14**, 1894 (1960).
[70] E. Andersen, E. A. Birkhimer, and T. A. Bak, *Acta Chem. Scand.* **14**, 1899 (1960).
[71] S. Patai and Y. Gotshal, *J. Chem. Soc.* **B**, 489 (1966).
[72] R. Nietski and R. Dietschy, *Ber. Deut. Chem. Ges.* **34**, 55 (1901).
[73] W. Will, *Ber. Deut. Chem. Ges.* **47**, 704 (1914).
[74] M. Giua, *Gazz. Chim. Ital.* **53**, 657 (1923).
[75] A. S. Bailey, M. Maung, G. W. F. Orpwood, and J. E. White, *Tetrahedron* **22**, 995 (1966).
[76] S. V. Bogdanov and M. V. Gorelik, *Khim. Nauka i Promy.* **3**, 279, 407 (1958).
[76a] S. V. Bogdanov and M. V. Gorelik, *Chem. Abstr.* **52**, 20089, 20135 (1958).

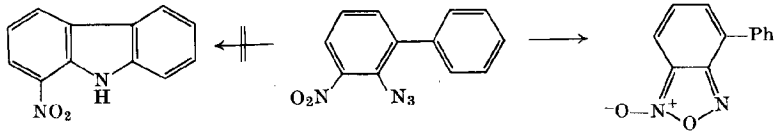
V. Substituted Benzofuroxans: Reactions of Substituents

A table listing the benzofuroxans known to the authors, from the literature or otherwise, with their melting points, appears in Section X, at the end of this chapter. The present section presents a brief summary of the presently available types of substituent groups on the benzene nucleus, and of the reactions they undergo.

A. Alkyl and Aryl Benzofuroxans

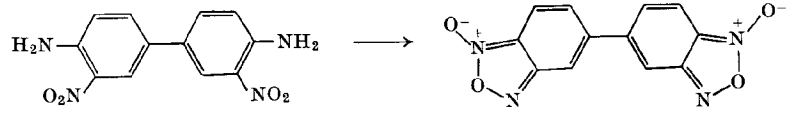
A number of alkyl and dialkyl (mainly methyl) benzofuroxans are known. The 4-methyl compound resisted attempts to brominate the methyl group and to oxidize it to the carboxylic acid.[77]

4-Phenylbenzofuroxan (**22**) is formed on pyrolysis or photolysis of 2-azido-3-nitrobiphenyl: the alternative mode of cyclization—to 4-nitrocarbazole—was not observed.[65]



(**22**)

Hetero-substituted 4,7-diarylbenzofuroxans (Section V,C) are known. The only representative 5-arylbenzofuroxan in Table I is 5,5′-bisbenzofuroxanyl (**23**), prepared from 4,4′-diamino-3,3′-dinitrobiphenyl by oxidation with hypochlorite.[56]



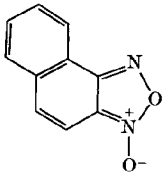
(**23**)

B. Annellated Benzofuroxans

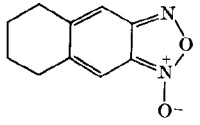
The 4,5-benzo-fused compound, 1,2-naphthofuroxan (**24**) was the first compound in the benzofuroxan series to be prepared[6,7]; the

[77] A. J. Boulton and P. B. Ghosh, unpublished work, 1964–1965.

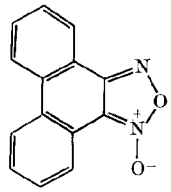
isomeric 2,3-naphthofuroxan, by contrast, is still unknown,[78] although its tetrahydro (**25**)[18] and octahydro[79] derivatives are known. The bisbenzo compound, 9,10-phenanthrenofuroxan (**26**) is also well established,[79] and an anthracenofuroxan has been reported.[76]



(**24**)



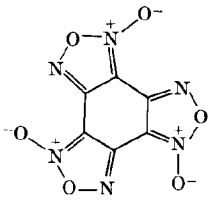
(**25**)



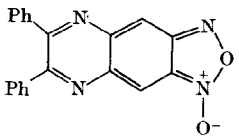
(**26**)

There are several instances of heterocyclic ring annellation, including 4,5-furoxano[36, 80, 81, 82] and 4,5-furazano[36] ring fusion (**17** and **18**), and the bisfuroxano derivative trisfuroxanobenzene (benzotrifuroxan, **27**)[22, 83]. The last compound readily forms charge transfer complexes with aromatic π-electron donors.[22, 84]

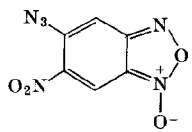
5,6-Ring fusion seems to occur in the quinoxaline derivative (**28**), which has been stated to exist in red and blue-black forms.[85] Other derivatives of type **28** are reported.[85] Attempts to prepare 5,6-furoxanobenzofuroxan by pyrolysis of the azide (**29**) met with no success.[19] An early example in the literature[80] of such a linear fused structure was shortly afterward revised[81] to the angularly fused type (**17**).



(**27**)



(**28**)

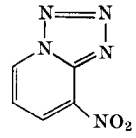


(**29**)

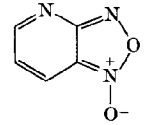
[78] Several attempts to make this compound by pyrolysis of 2-azido-3-nitronaphthalene failed (ref. 35).
[79] J. H. Boyer and U. Toggweiler, *J. Am. Chem. Soc.* **79**, 895 (1957).
[80] H. Goldschmidt and J. Strauss, *Ber. Deut. Chem. Ges.* **20**, 1607 (1887).
[81] H. Goldschmidt, *Ber. Deut. Chem. Ges.* **22**, 3101 (1889).
[82] R. Nietzki and W. Geese, *Ber. Deut. Chem. Ges.* **32**, 506 (1899).
[83] O. Turek, *Chim. Ind. (Paris)* **26**, 781 (1931).
[84] A. S. Bailey, *J. Chem. Soc.* p. 4710 (1960).
[85] J. H. Boyer and R. S. Buriks, *J. Am. Chem. Soc.* **82**, 2216 (1960).

C. Heterosubstituted Benzofuroxans

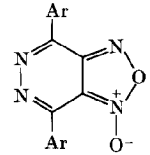
Pyrido[2,3-*c*]furoxan (4-azabenzofuroxan, **31**) is prepared by pyrolysis of the nitropyridotetrazole (**30**)[18] (concerning its tautomerism, see Section III,C). Some derivatives of **31** are also known[86] (see Table I). Unsuccessful attempts to make pyrido[3,4-*c*]furoxan and its *N*-oxide have been reported,[34, 87, 88] although its 7-nitro[88, 89] and 6,7-benzo (**16**)[35] derivatives have been prepared. Hydrazine and 3,4-diaroylfuroxans give the diarylpyridazinofuroxans (**32**).[90]



(**30**)



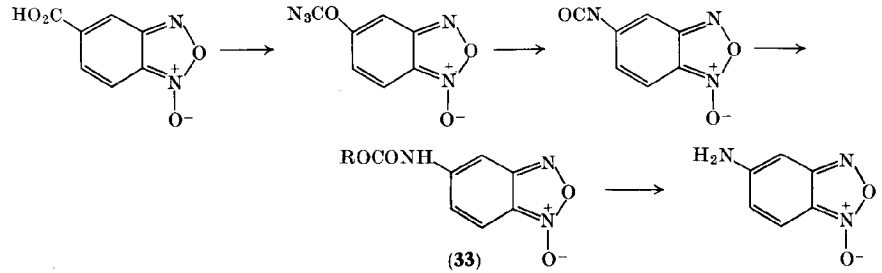
(**31**)



(**32**)

D. Amino- and Acylaminobenzofuroxans

Early attempts to prepare 5-amino- and 5-acylaminobenzofuroxans by hypochlorite oxidation of the corresponding *o*-nitroanilines met with failure.[58] Pyrolysis of the appropriate azide, however, gives 5-dimethylamino- and 5-acetamidobenzofuroxan, whereas urethans of type (**33**) are produced by Curtius degradation of the 5-carboxylic acid. Controlled hydrolysis of the acetamido compound and the



(**33**)

[86] J. H. Boyer and W. Schoen, *J. Am. Chem. Soc.* **78**, 423 (1956).
[87] J. H. Boyer and S. Kruger, *J. Am. Chem. Soc.* **79**,.3552 (1957).
[88] M. W. Heaton, B. Sc. Thesis, Oxford University, 1963; J. I. Murphy, B. Sc. Thesis, Oxford University, 1965.
[89] R. T. Aplin and W. T. Pike, *Chem. Ind. (London)* p. 2009 (1966). In this paper the nitro group was omitted from the pyridofuroxan formula.
[90] H. R. Snyder and N. E. Boyer, *J. Am. Chem. Soc.* **77**, 4233 (1955).

urethans gave the unstable 5-aminobenzofuroxan, with an ultraviolet spectrum similar to that of the 5-dimethylamino compound.[27]

An attempt at Hofmann degradation of 4-carboxamidobenzofuroxan failed to give any 4-amino compound.[91] Nitro groups appear to stabilize aminobenzofuroxans, however; 4-amino-5-nitro,[91] 5-anilino-6-nitro-[22] and several substituted 4-amino-7-nitro- and 5-amino-4-nitrobenzofuroxans[92] have been isolated.

The preparation of 5,6-diaminobenzofuroxan, by decomposition of 1,2-diamino-4-azido-5-nitrobenzene, has been reported.[93]

E. Hydroxybenzofuroxans and Derivatives

Attempts to prepare 5-hydroxybenzofuroxan by demethylation of 5-methoxybenzofuroxan,[27] by pyrolysis of 4-azido-3-nitrophenol,[27] and by hypochlorite oxidation of 4-amino-3-nitrophenol[58] failed. This rather unstable compound was finally prepared by hydrolysis of 5-acetoxybenzofuroxan; its tautomeric possibilities are numerous, but from the similarity of its ultraviolet spectrum to that of 5-methoxybenzofuroxan it was considered to be largely in the hydroxy form.[27] It is a fairly strong acid, of pK 6.75 (cf. 5-hydroxybenzofurazan,[94] pK 7.28). 7-Hydroxy-4,6-dinitrobenzofuroxan has been reported as arising from oxidation and nitration of dinitrosoresorcinol monooxime (tetraoxocyclohexene trioxime).[95]

Acyloxy derivatives are known, in the 5-acetoxy compound mentioned above,[27] and 5-benzoyloxybenzofuroxan.[96]

Alkoxybenzofuroxans are well-known, and the hypochlorite oxidation method is usually used for their preparation. For the formation of haloalkoxybenzofuroxans from nitrobenzofuroxans, see Section VII,B.

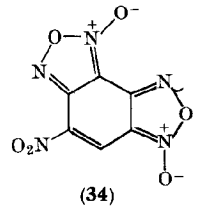
[91] A. J. Boulton, P. B. Ghosh, and A. R. Katritzky, *J. Chem. Soc.* **B**, 1004 (1966).
[92] P. B. Ghosh, *J. Chem. Soc.* **B**, 334 (1968).
[93] J. H. Boyer, R. S. Buriks, and U. Toggweiler, *J. Am. Chem. Soc.* **82**, 2213 (1960).
[94] D. Dal Monte and E. Sandri, *Ann. Chim.* (*Rome*) **54**, 486 (1964).
[95] W. Borsche and H. Weber, *Ann. Chem.* **489**, 270 (1931).
[96] D. Dal Monte Casoni and E. Sandri, Belgian Patent No. 660,379 (1965); *Chem. Abstr.* **64**, 2098 (1966).

F. Halobenzofuroxans

Many chloro- and bromo-, but no fluoro- or iodobenzofuroxans have been described. The halogen atom may be displaced by nucleophiles, provided that it is activated by the presence of a nitro group.[36, 92, 97]

G. Nitrobenzofuroxans

Nitration of benzofuroxans (Section VII,A) and decomposition of polynitrophenyl azides, provide generally satisfactory routes to nitrobenzofuroxans. The nitro groups render the ring susceptible to nucleophilic attack (see Section VII,B). 4,6-Dinitrobenzofuroxan, 5,6-dinitrobenzofuroxan, and nitrobenzodifuroxan (**34**) act as acceptors in change-transfer complex formation with aromatic hydrocarbons.[22] Nitrobenzofuroxans have not been reduced to the



(**34**)

amino derivatives, since the furoxan ring is apparently more susceptible to reduction than the nitro groups; in some cases nitrodiamines have been formed by partial reduction, the original nitro groups remaining intact,[93] and 5-nitrobenzofurazan has been prepared by triphenyl phosphine reduction of the furoxan.[37]

Nucleophilic displacement of a nitro group by aniline in 5,6-dinitrobenzofuroxan has been reported.[22] Rearrangements of 4-nitrobenzofuroxans are discussed in Section VIII.

H. Acyl- and Carboxy-Substituted Benzofuroxans

Derivatives of benzofuroxan-4- and 5-carboxylic acids are known, and the acids themselves (see Section X). Their degradation to the corresponding amino derivatives is discussed in Section V,D.

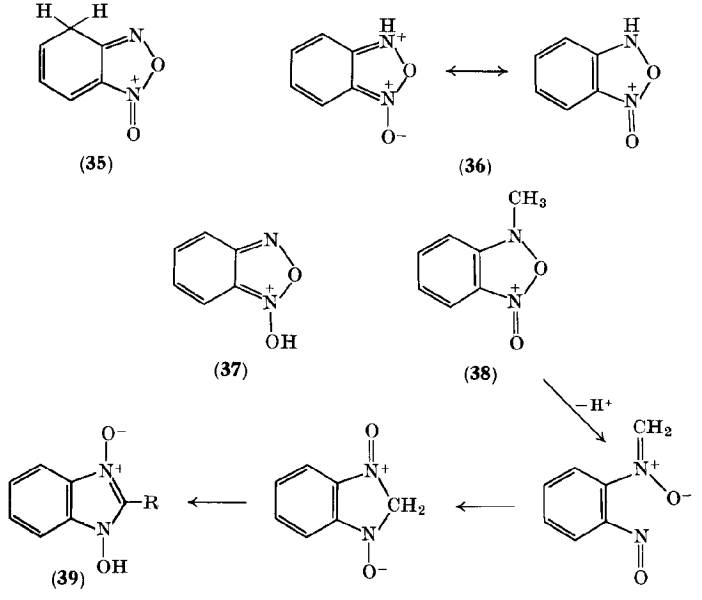
[97] A. J. Boulton, A. C. Gripper Gray, and A. R. Katritzky, *J. Chem. Soc.* **B**, 909 (1967).

5-Formylbenzofuroxan has been prepared,[77] but the 4-acetyl compound rearranges under the conditions used for its preparation, to an anthranil derivative (see Section VIII).

VI. Reactions of the Heterocyclic Ring

A. Electrophilic Attack

Although the ultraviolet spectrum of benzofuroxan undergoes an extensive, and reversible, change on solution in fairly concentrated sulfuric acid, suggesting that protonation is occurring, the site of proton attachment is not known. Benzofuroxans behave approximately as Hammett bases (Gr. $(\log_{10}[BH^+]-\log_{10}[B])/H_0=1$), with pK_a's -8.3 ± 0.1 (unsubst.), -8.4 ± 0.1 (4-Me), -8.2 ± 0.1 (5-Me) (cf. -8.4 ± 0.1 for benzofurazan).[34] *C*-Protonation (as **35**) would probably require the protonation to follow a steeper acidity function (cf. azulenes[98, 99]), and therefore *N*- (**36**) or *O*- (**37**) protonation is indicated. pK_a values have also been quoted for the 5-amino (+0.5) and 5-dimethylamino (+1.2) compounds,[27] but a recent reinvestigation[100] showed that the spectral changes occurring on acidification of the latter compound are not reversible, suggesting that decomposition had taken place.



(35) (36) (37) (38) (39)

Quaternization is difficult; benzofuroxan is unaffected by triethyloxonium fluoroborate.[101, 101a] With methyl trifluoromethanesulfonate, an interesting rearrangement occurs, and 1-hydroxybenzimidazole-3-oxide (**39**, R = H) is formed, probably via the *N*-quaternized derivative (**38**). Compound **39** ($R=C_6H_5$) has been prepared similarly.[101, 101a]

B. Oxidation

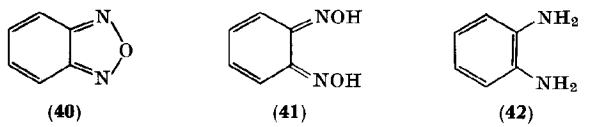
Benzofuroxan and 5-methylbenzofuroxan are oxidized by trifluoroperacetic acid to *o*-dinitrobenzene and 3,4-dinitrotoluene, respectively.[102] 4-Nitro- and 4,6-dinitrobenzofuroxan are unaffected by this reagent, whereas the 5-chloro and 5-methoxy compounds are destroyed.[102] Milder reagents (performic, peracetic acids) do not oxidize benzofuroxans.[22]

C. Reduction

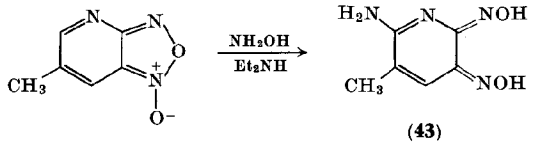
The reduction of benzofuroxans can lead to a variety of products, depending upon the conditions. Deoxygenation to benzofurazans (**40**) can be effected either directly, using trialkyl phosphites,[36, 97, 103] tributyl[103] or triphenyl[37, 103] phosphine, or indirectly, via *o*-quinone dioximes (**41**), using methanol and potassium hydroxide,[5] or hydroxylamine and alkali.[8, 9, 48, 56, 58, 86, 104] The dioximes may be isolated, but if the benzofurazan is required it is usually obtained by steam distillation of the alkaline reaction mixture.[8, 56, 104] In addition, amination occurs with 6-methylpyrido[2,3-*c*]furoxan, giving 3-aza-4-amino-5-

[98] E. Heilbronner, *in* "Non-benzenoid Aromatic Compounds" (D. Ginsburg, ed.), p. 260. Wiley (Interscience), New York, 1959.
[99] F. A. Long and J. Schulze, *J. Am. Chem. Soc.* **86**, 327 (1964).
[100] A. J. Boulton and P. J. Halls, unpublished work, 1967.
[101] A. J. Boulton, A. C. Gripper Gray, and A. R. Katritzky, *Chem. Commun.* p. 741 (1966).
[101a] A. J. Boulton, A. C. Gripper Gray, and A. R. Katritzky, *J. Chem. Soc.* **B**, 911 (1967).
[102] J. H. Boyer and S. E. Ellzey, *J. Org. Chem.* **24**, 2038 (1959).
[103] J. H. Boyer and S. E. Ellzey, *J. Org. Chem.* **26**, 4684 (1961).
[104] D. Dal Monte Casoni and E. Sandri, *Ann. Chim.* (*Rome*) **53**, 1697 (1963).

methyl-*o*-benzoquinone dioxime (**43**).[86] Naphtho[1,2-*c*]furoxan is reported to give the corresponding furazan with hydrazine.[10] Sodium borohydride gives the dioxime or the benzofurazan, depending upon the temperature,[105] while hydriodic acid has been reported to give

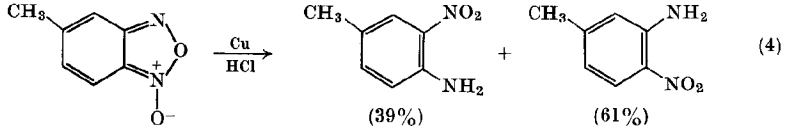


(**40**) (**41**) (**42**)



(**43**)

the diamine (**42**), in some cases.[93] Benzofuroxans are reduced to *o*-phenylenediamines with lithium aluminum hydride,[106] tin and hydrochloric acid,[48,66] hydrogen and platinum,[38] hydrazine hydrate,[10] and alkali metal sulfides in alcohol.[18,107] The action of copper and hydrochloric acid produces *o*-nitroanilines in quantitative yield[12,38,39]; with 5-methylbenzofuroxan both aminonitrotoluenes were obtained [Eq. (4)]. It has been suggested that the reaction takes place via a copper chelate.[12]



(4)

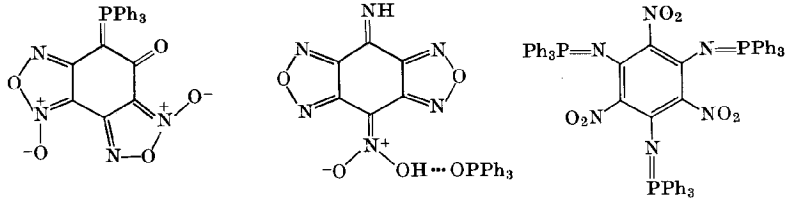
(39%) (61%)

Some internal oxidation–reduction reactions have been reported with the bisulfite adducts of naphtho[1,2-*c*]furoxan[108–110] and some

[105] J. H. Boyer and S. E. Ellzey, *J. Am. Chem. Soc.* **82**, 2525 (1960).
[106] A. Dornow, K. J. Fust, and H. D. Jordan, *Chem. Ber.* **90**, 2124 (1957).
[107] K. Fries and K. Noll, *Ann. Chem. Liebigs* **389**, 367 (1912).
[108] S. V. Bogdanov and I. N. Koroleva, *Zh. Obshch. Khim.* **23**, 1761 (1953); *Chem. Abstr.* **48**, 13658 (1954).
[109] S. V. Bogdanov and I. N. Koroleva, *Zh. Obshch. Khim.* **24**, 1994 (1954); *J. Gen. Chem. USSR* **24**, 1989 (1954); *Chem. Abstr.* **49**, 13977 (1955).
[110] M. V. Gorelik, *in* "Organicheskie Poluprodukti i Krasiteli. Vol. **3**: Sul'firovanie Solyami Sernistoi Kisloti—Reaktsii Bogdanova," pp. 90–119. Khimiya, Moscow, 1965.

of its derivatives,[110–112] leading to nitroamines, naphthofurazans, or 1,2-naphthoquinone dioxime derivatives, depending upon the conditions.

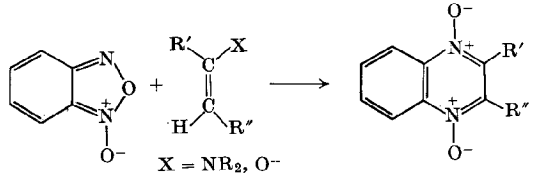
Curious products isolated by Bailey and Evans from the reaction of benzotrisfuroxan with triphenyl phosphine have been examined by X-ray crystallography by Cameron and Prout. The structures (**44–46**) were determined.[113,114] A molecular complex of trialkyl phosphate with benzotrisfurazan is formed using a trialkyl phosphite as reducing agent.[115,115a]



(**44**) (**45**) (**46**)

D. Miscellaneous Reactions

A variety of enamines[116] and enolate anions[117] have been found to react with benzofuroxan, giving quinoxaline di-*N*-oxides in moderate yields [Eq. (5)].



(5)

X = NR_2, O^-

[111] S. V. Bogdanov and N. I. Zil'berman, *Zh. Obshch. Khim.* **26**, 2071 (1956); *J. Gen. Chem. USSR* **26**, 2311 (1956); *Chem. Abstr.* **51**, 5056 (1957).
[112] S. V. Bogdanov and Z. V. Todres-Selektor, *Zh. Vses. Khim. Obshchestva im. D.I. Mendeleeva* **7**, 697 (1962); *Chem. Abstr.* **58**, 9053 (1963).
[113] A. S. Bailey, T. S. Cameron, J. M. Evans, and C. K. Prout, *Chem. Commun.* p. 664 (1966).
[114] T. S. Cameron and C. K. Prout, *Chem. Commun.* p. 455 (1967).
[115] A. S. Bailey and J. M. Evans, *Chem. Ind. (London)* p. 1424 (1964).
[115a] A. S. Bailey and J. M. Evans, *J. Chem. Soc.* **C**, 2105 (1967).
[116] M. J. Haddadin and C. H. Issidorides, *Tetrahedron Letters* p. 3253 (1965).
[117] C. H. Issidorides and M. J. Haddadin, *J. Org. Chem.* **31**, 4067 (1966).

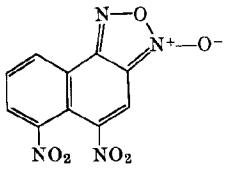
For rearrangements involving the heterocyclic ring, see Sections II; III, C; and VIII.

VII. Reactions of the Homocyclic Ring

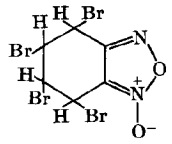
A. Electrophilic Attack

Nitration proceeds readily in benzofuroxan, giving first the 4-nitro, then the 4,6-dinitro compound.[58, 118] 5-Nitrobenzofuroxan, according to Drost,[118] is nitrated further in the adjacent 6-position. Bailey and Case[22] reported that the major product is the 4,6-dinitro compound, but they did succeed in isolating a small amount of the 5,6-dinitro derivative from the reaction.

5-Chloro- and 5-methylbenzofuroxans are readily nitrated in the 4-position; the product rearranges easily to form 7-substituted 4-nitro compounds (see Section VIII), also obtained by nitration of the corresponding 4-substituted benzofuroxans.[25, 119] Dinitration of 5-methylbenzofuroxan is said to give a product of m.p. 133°, while the 4-methyl gives a dinitro compound m.p. 122°–123°.[120] For other benzofuroxans to have been nitrated see refs. 19, 36, 81, 97, 121. There appears to be some confusion over the site of electrophilic substitution of naphtho[1,2-*c*]furoxan. Early reports in the literature state that nitration gives the 5,6-dinitro derivative (**47**).[58, 122] However, sulfona-



(**47**)



(**48**)

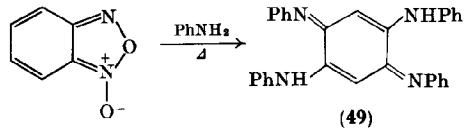
[118] P. Drost, *Ann. Chem.* **307**, 49 (1899).
[119] P. Drost, *Ann. Chem.* **313**, 299 (1900).
[120] W. B. Hardy and R. A. Parent, French Patent No. 1,395,886 (1965); *Chem. Abstr.* **63**, 14875 (1965).
[121] Netherlands Patent Appl. No. 6,510,031 (1965) (to Shell Internationale Research, Maatschappij, N.V.); *Chem. Abstr.* **64**, 11216 (1966).
[122] G. Ponzio, *Gazz. Chim. Ital.* **36 II**, 316 (1906). The authors of Ref. 58 were responsible for the assignment of structure **47** to the product, on very slender evidence.

tion and chlorination both lead to 4-substituted compounds[123] and the nitration work should be regarded with suspicion. Di- and trinitro derivatives of 8-hydroxynaphtho[1,2-*c*]furoxan have been reported.[124]

Other electrophilic substitutions proceed with difficulty, or not at all. Nitrosation and diazo coupling require the presence of the strongly activating dimethylamino group (see Section VIII). Bromine adds, in the presence of sunlight, to give tetrabromotetrahydrobenzofuroxan (**48**); the initial attack is probably free-radical in nature. The product can be dehydrobrominated to form 4,7-, or a mixture of 4,5- and 4,6-dibromobenzofuroxan, depending upon the conditions.[5, 125] More conventional electrophilic bromination conditions have been tried in an attempt to obtain a monosubstituted product, but without success.[125a]

B. Nucleophilic Attack

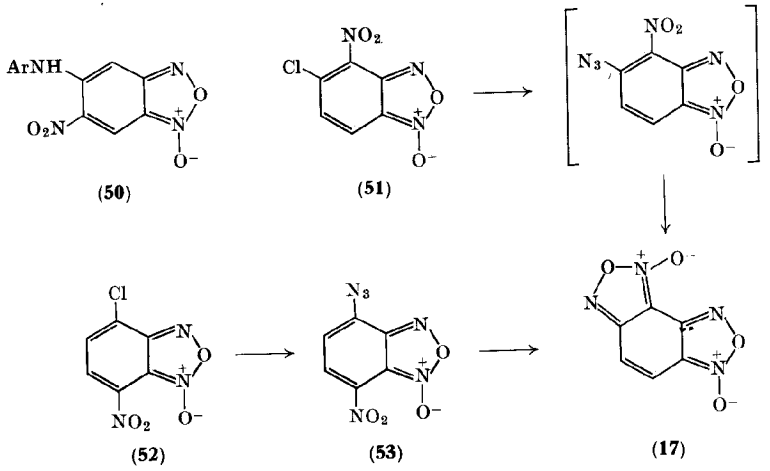
Aniline and benzofuroxan react at high temperatures (150°–160°) to give 2,5-dianilinobenzoquinone dianil (**49**).[126] *o*-Phenylenediamine gives a diaminophenazine.[48]



(**49**)

Several examples of nucleophilic displacement of nitro-activated leaving groups have been recorded. 5,6-Dinitrobenzofuroxan with aniline and *p*-bromoaniline gives the corresponding substitution product (**50**).[22, 118] Azide ion displaces chloride from both 5-chloro-4-nitro- and 4-chloro-7-nitrobenzofuroxan (**51** and **52**); the product from the former loses nitrogen spontaneously to give furoxanobenzofuroxan (benzobisfuroxan, **17**), which is also formed, although in poor

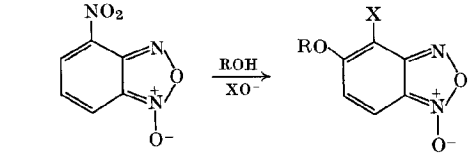
[123] S. V. Bogdanov and I. N. Koroleva, *Zh. Obshch. Khim.* **26**, 243 (1956); *J. Gen. Chem. USSR* **26**, 269 (1956); *Chem. Abstr.* **50**, 13884 (1956).
[124] R. Nietzki and T. Knapp, *Ber. Deut. Chem. Ges.* **30**, 1119 (1897).
[125] W. Moje, *J. Org. Chem.* **29**, 3722 (1964).
[125a] D. P. Clifford, M.Sc. Thesis, University of East Anglia, 1965.
[126] P. Ruggli and F. Buchmeier, *Helv. Chim. Acta* **28**, 850 (1945).



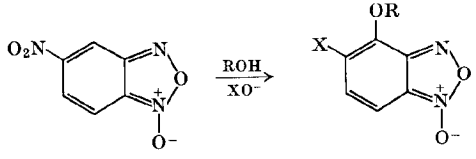
(50) (51) (52) (53) (17)

yield, on heating (**53**).[36] Other nucleophiles (RO^-, RR'NH, RS^-) can also displace the halide in compounds **51** and **52**.[92, 121]

Nitrobenzofuroxans with alcoholic hypochlorite or hypobromite undergo an interesting reaction, the haloalkoxy substitution reaction, in which the nitro group is replaced by halogen, and an alkoxy group appears at an adjacent *ortho* position [Eqs. (6) and (7), R = Me or Et, X = Cl or Br].[38, 39] These reactions had essentially been discovered earlier[8, 60] (using dinitroaniline precursors of the starting benzofuroxans), but in each case the substitution pattern had been incorrectly assigned.

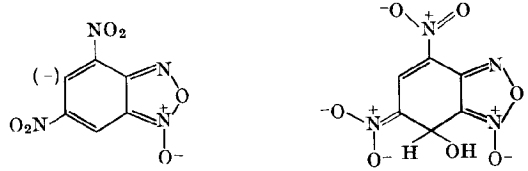


(6)



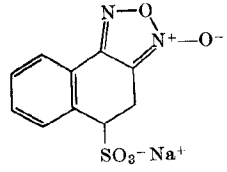
(7)

4,6-Dinitrobenzofuroxan dissolves slightly in water, giving an acid reaction, and forms a series of explosive[118, 127] salts which were originally[118] formulated as containing the anion (**54**). Acidification regenerates the dinitro compound. It has recently been shown that the anion is, in fact, the Meisenheimer complex (**55**), on infrared, NMR, and chemical evidence,[26, 128, 129] including the use of ^{18}O and ^{2}H. Dinitronaphtho[1,2-*c*]furoxan is also reported to form a mildly explosive salt.[58] An anilide of 4,6-dinitrobenzofuroxan, of uncertain structure, is also known.[118] Naphtho[1,2-*c*]furoxan does not form an



(54) (55)

adduct with sodium bisulfite; **56**, commonly called sodium naphthofuroxan bisulfite, is prepared by oxidation of the oxime of the bisulfite compound of 1-nitroso-2-naphthol.[108–110]



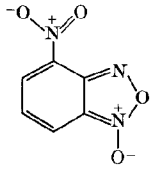
(56)

VIII. Rearrangements

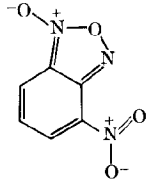
The 1-oxide ⇌ 3-oxide tautomerism [Eq. (3), p. 4] has been discussed earlier (Sections II and III,C) in connection with the problem of the structure of benzofuroxan. A second type of rearrangement involves the furoxan ring and an adjacent substituent group, and arose out of a suggestion of Bailey and Case[22] that 4-nitrobenzofuroxan might be a resonance hybrid of type (**57**) ↔ (**58**), rather than **57**. NMR ruled out this possibility: the three protons present in

[127] H. Rathsburg, *Z. Angew. Chem.* **41**, 1284 (1928).
[128] N. E. Brown and R. T. Keyes, *J. Org. Chem.* **30**, 2452 (1965).
[129] A. J. Boulton and D. P. Clifford, *J. Chem. Soc.* p. 5414 (1965).

the molecule all absorbed at different chemical shifts (an ABC pattern, rather than AB_2), and a fast tautomerism (**57** $\rightleftharpoons$ **58**) apparently did not occur, even at 160°C.[13] **57** and **58** therefore interconverted slowly or not at all. The isolation of substituted derivatives (**59**, $R_1 = CH_3$

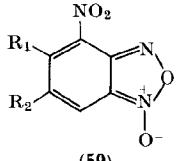


(57)

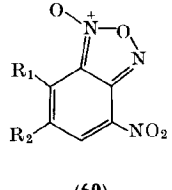


(58)

and Cl, $R_2 = H$) and their conversion into the isomeric compounds (**60**, $R_1 = CH_3$ and Cl, $R_2 = H$) showed that the rearrangement did, in fact, occur.[25] The reaction goes apparently to completion in the two cases cited; steric inhibition of resonance of the nitro group in compounds **59** seemingly plays an important part in increasing their energy over that of **60**. Ultraviolet evidence also suggested that the two systems are not electronically identical. This rearrangement sometimes proceeds very readily, and has resulted in the misassignment of structures to a number of benzofuroxan nitration products in

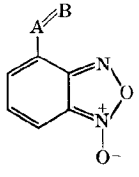


(59)

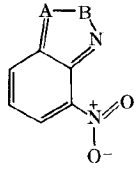


(60)

the literature.[19, 119, 120] The reverse reaction (**60** $\rightarrow$ **59**) probably occurs during the formation of the bisfuroxan (**17**) from the azide

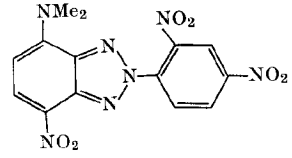


(61)

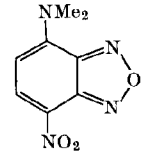


(62)

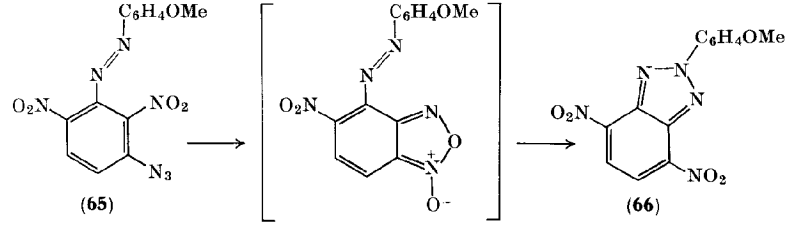
(**53**; $\equiv$ **60**; $R_1 = N_3$, $R_2 = H$),[36] and an equilibrium is observed in the case of the deuterated compound (**59**; $R_1 = {}^2H$, $R_2 = NO_2$).[128] Certain secondary amino-substituted compounds (**59**, **60**; $R_1 = RNH$, $R_2 = H$) show solvent dependence of their equilibria; solutions in dimethyl sulfoxide contain mainly form **59**, whereas alcohols as solvents favor form **60**.[92]



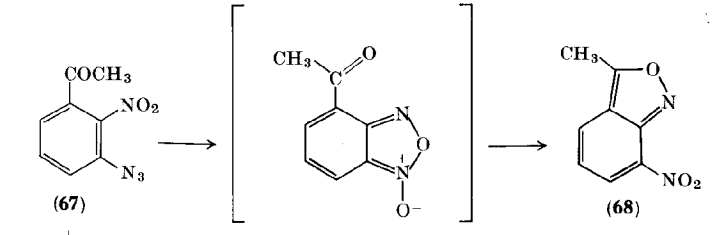
(63)



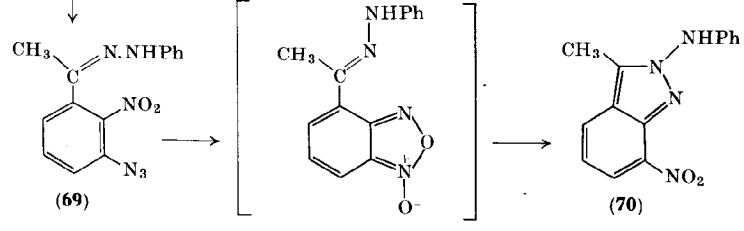
(64)



(65) (66)



(67) (68)



(69) (70)

The rearrangement has been extended to other 4-substituted benzofuroxans of type **61**, giving **62**[91, 130–132]; although in no case to date has the benzofuroxan been isolated, they are presumed intermediates in the formation of **63** and **64** from 5-dimethylaminobenzofuroxan with 2,4-dinitrobenzenediazonium chloride and nitrous acid, respectively,[131] and of **66** from **65**,[131] **68** from **67**,[132] and **70** from **69**.[132]

IX. Uses

Reduction of benzofuroxans is usually the most convenient route to benzofurazans and *o*-quinone dioximes (see Section VI,C). Reduction of 4-nitrobenzofuroxan would seem to be a method of synthesis of 1,2,3-triaminobenzene, while the haloalkoxy-substitution reaction (Section VII,B) and the rearrangements of Section VIII provide compounds accessible only with difficulty by other methods. Apart from these reactions, the benzofuroxans appear to be of limited synthetic utility.

A few commercial applications of benzofuroxans have been suggested in the Patent literature and elsewhere. A wide range of biological activity (fungicidal or fungistatic,[133–137] bactericidal,[133, 134] parasiticidal,[134] and insecticidal[121, 133, 134, 138]) has been claimed for benzofuroxan and some of its derivatives. In other fields, the explosive properties of alkali-metal salts of 4,6-dinitrobenzofuroxan[127] have led to its being patented for use in detonators,[139] while benzofuroxan has been proposed as a photographic desensitizer,[140] and it and a number of its derivatives have been tested for use as depolarizers in electric cells,[120, 141, 142] and as antiskinning agents in drying oil compositions.[143]

[130] A. J. Boulton, P. B. Ghosh, and A. R. Katritzky, *Angew. Chem.* **76**, 816 (1964); *Angew. Chem. Intern. Ed. English* **3**, 693 (1964).
[131] A. J. Boulton, P. B. Ghosh, and A. R. Katritzky, *J. Chem. Soc.* **B**, 1004 (1966).
[132] A. J. Boulton, P. B. Ghosh, and A. R. Katritzky, *J. Chem. Soc.* **B**, 1011 (1966).
[133] W. P. Ter Horst, U.S. Patent No. 2,302,384 (1942); *Chem. Abstr.* **37**, 2507 (1943).
[134] W. P. Ter Horst, U.S. Patent No. 2,424,199 (1947); *Chem. Abstr.* **41**, 7642 (1947).
[135] G. Tappi and P. V. Forni, *Farm. Sci. Tec.* (*Pavia*) **5**, 241 (1950); *Chem. Abstr.* **44**, 9103 (1950).
[136] G. Tappi and P. V. Forni, *Chim. Ind.* (*Milan*) **33**, 135 (1951); *Chem. Abstr.* **45**, 9804 (1951).
[137] Netherlands Patent Appl. 6,400,307 (1965) (to N.V. Philips' Gloeilampenfabrieken); *Chem. Abstr.* **63**, 17071 (1965).
[138] D. Dal Monte Casoni and E. Sandri, Belgian Patent No. 660,379 (1965); *Chem. Abstr.* **64**, 2098 (1966).

X. Table of Benzofuroxans

The following table lists the benzofuroxan derivatives, with their melting points, which the authors have been able to find in the published literature. No attempt has been made to provide an exhaustive reference list; those quoted are intended to be selected for their preparative usefulness. Substituents in parentheses indicate that a ring CH group, rather than a H atom, is replaced. Additional references (144–149) not cited earlier in the text are to be found at the foot of this page.

ACKNOWLEDGMENT

We thank Dr. M. V. Gorelik, Ministry of Chemical Industry, Moscow, for helpful correspondence.

[139] R. McGirr, U.S. Patent No. 3,135,636 (1964); *Chem. Abstr.* **61**, 5446 (1964).
[140] G. F. Duffin, U.S. Patent No. 3,050,395 (1962); *Chem. Abstr.* **58**, 164 (1963).
[141] W. B. Hardy and R. A. Parent, U.S. Patent No. 3,163,561 (1964); *Chem. Abstr.* **64**, 3559 (1966).
[142] J. T. Shaw, J. D. Voorhies, and S. M. Davis, French Patent No. 1,374,790 (1964); *Chem. Abstr.* **62**, 7769 (1965).
[143] R. H. Rosenwald, U.S. Patent No. 2,630,438 (1953); *Chem. Abstr.* **47**, 5698 (1953).
[144] E. Muller and K. Weisbrod, *J. Prakt. Chem. Ser.* **2**, **113**, 30 (1926).
[145] P. Karrer, *Ber. Deut. Chem. Ges.* **46**, 253 (1913).
[146] P. B. Ghosh and M. W. Whitehouse, *J. Med. Chem.* **11**, 305 (1968).
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TABLE I

BENZOFUROXAN AND ITS DERIVATIVES

Molecular formula	Substituent at position 4	5	6	7	Melting point (°C)	Ref.
$C_5H_2N_3O_4$	NO_2	—	(N)	—	134[d]	88
$C_5H_3N_4O_2$	(N)	—	—	—	52–53	86
$C_6N_6O_6$	$=N_2O_2=$[a]		$=N_2O_2=$		192–194	22
$C_6HDN_4O_6$	NO_2	D	NO_2	—	170[b]	128
$C_6HDN_4O_6$	NO_2	—	NO_2	D	*b, c, e*	128
$C_6HCl_2N_3O_4$	NO_2	Cl	Cl	—	97–100[d]	146
$C_6HN_5O_6$	$=N_2O_2=$		NO_2	—	158	19, 22
$C_6H_2Br_2N_2O_2$	Br	Br	—	—	148–149	125
$C_6H_2Br_2N_2O_2$	Br	—	Br	—	92.5–93	125
$C_6H_2Br_2N_2O_2$	Br	—	—	Br	132	21
$C_6H_2Br_2N_2O_2$	—	Br	Br	—	128–128.5	125
$C_6H_2ClN_3O_4$	NO_2	Cl	—	—	78–81[d]	25
$C_6H_2ClN_3O_4$	—	Cl	NO_2	—	88–89	22
$C_6H_2Cl_2N_2O_2$	Cl	—	Cl	—	107–108	146
$C_6H_2Cl_2N_2O_2$	Cl	—	—	Cl	96.6–97	14
$C_6H_2Cl_2N_2O_2$	—	Cl	Cl	—	130.8–131.2	14
$C_6H_2N_4O_3$	$=N_2O=$[f]		—	—	50–60	36
$C_6H_2N_4O_4$	$=N_2O_2=$		—	—	94–95	36
$C_6H_2N_4O_6$	NO_2	—	NO_2	—	172	118
$C_6H_2N_4O_6$	NO_2	—	—	NO_2	170–172	95
$C_6H_2N_4O_6$	—	NO_2	NO_2	—	177	22
$C_6H_2N_4O_7$	OH	NO_2	—	NO_2	132–133	95
$C_6H_2N_6O_4$	NO_2	—	—	N_3	118–119[d]	34, 36
$C_6H_2N_6O_4$	—	NO_2	N_3	—	90[d]	19, 22
$C_6H_3DN_2O_2$	—	D	—	—	*e*	128
$C_6H_3BrN_2O_2$	Br	—	—	—	105	57
$C_6H_3BrN_2O_2$	—	Br	—	—	69	10
$C_6H_3ClN_2O_2$	Cl	—	—	—	77–77.5	60
$C_6H_3ClN_2O_2$	—	Cl	—	—	48	9
$C_6H_3N_3O_4$	NO_2	—	—	—	143	118
$C_6H_3N_3O_4$	—	NO_2	—	—	72	66
$C_6H_3N_3O_4$	(N)	—	COOH	—	173.5–175[d]	86
$C_6H_4N_2O_2$	—	—	—	—	72	51, 52
$C_6H_4N_2O_3$	—	OH	—	—	*d, e*	27
$C_6H_4N_4O_4$	NH_2	NO_2	—	—	250[d]	91
$C_6H_5AsN_2O_5$	—	AsO_3H_2	—	—	*e*	145
$C_6H_5N_3O_2$	(N)	—	CH_3	—	85.5–86.5	86
$C_6H_5N_3O_2$	(N)	—	—	CH_3	74–75.5	100
$C_6H_5N_3O_2$	—	NH_2	—	—	*d, e*	27
$C_6H_6N_4O_2$	—	NH_2	NH_2	—	*d, e, g*	93
$C_7H_3ClN_2O_3$	—	COCl	—	—	54–54.5	27
$C_7H_3N_3O_3$	—	NCO	—	—	150[d]	27
$C_7H_3N_5O_3$	—	CON_3	—	—	90–92	27
$C_7H_4N_2O_3$	—	CHO	—	—	68.5–69	146
$C_7H_4N_2O_4$	COOH	—	—	—	208–209	146
$C_7H_4N_2O_4$	—	COOH	—	—	130–130.5	27
$C_7H_4N_4O_4$	$=N_2O_2=$		CH_3	—	103	80
$C_7H_4N_4O_6$	CH_3	NO_2	—	NO_2	122–123[d]	119
$C_7H_4N_4O_6$	NO_2	CH_3	NO_2	—	133[d]	19
$C_7H_5BrN_2O_3$	Br	OMe	—	—	157.4–157.8	39
$C_7H_5BrN_2O_3$	OMe	Br	—	—	90–91	39
$C_7H_5ClN_2O_3$	Cl	OMe	—	—	134–134.8	38
$C_7H_5ClN_2O_3$	OMe	Cl	—	—	80.6–82	38
$C_7H_5N_3O_3$	$CONH_2$	—	—	—	180.5–181	91

TABLE I—*continued*

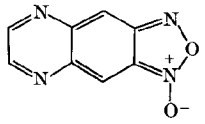
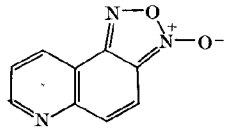
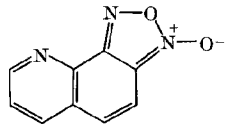
Molecular formula	Substituent at position 4	5	6	7	Melting point (°C)	Ref.
$C_7H_5N_3O_4$	(N)	—	COOMe	—	106.5–107.5	86
$C_7H_5N_3O_4$	CH_3	NO_2	—	—	71.5–72	132
$C_7H_5N_3O_4$	CH_3	—	NO_2	—	70	119
$C_7H_5N_3O_4$	CH_3	—	—	NO_2	162	25, 119
$C_7H_5N_3O_4$	NO_2	CH_3	—	—	100[d]	25
$C_7H_5N_3O_4$	—	CH_3	NO_2	—	67	75
$C_7H_5N_3O_4$	NO_2	—	CH_3	—	145	119
$C_7H_5N_3O_5$	OMe	—	—	NO_2	160–161	92
$C_7H_6ClN_3O_2$	—	NHMe	Cl	—	141–142	146
$C_7H_6N_2O_2$	CH_3	—	—	—	60	48
$C_7H_6N_2O_2$	—	CH_3	—	—	98	48
$C_7H_6N_2O_3$	OMe	—	—	—	125.5–126	60
$C_7H_6N_2O_3$	—	OMe	—	—	118	19
$C_8H_4N_4O_2$					>300[g,n]	85
$C_8H_6N_2O_4$	COOMe	—	—	—	147–148	91
$C_8H_6N_2O_4$	COOH	—	CH_3	—	210–212	91
$C_8H_6N_2O_4$	—	OAc	—	—	65–66	27
$C_8H_6N_4O_5$	NO_2	—	—	NHAc	209–210	92
$C_8H_6N_4O_6$	NHCOOMe	NO_2	—	—	195–197	91
$C_8H_7ClN_2O_3$	Cl	OEt	—	—	99.8–102	38
$C_8H_7ClN_2O_3$	OEt	Cl	—	—	51.8–53	38
$C_8H_7N_3O_3$	—	NHAc	—	—	177–179	27
$C_8H_7N_3O_4$	CH_3	NO_2	—	CH_3	81	107
$C_8H_7N_3O_4$	NO_2	CH_3	—	CH_3	116	119
$C_8H_8ClN_3O_2$	—	NMe_2	Cl	—	98–99	27
$C_8H_8N_2O_2$	CH_3	—	CH_3	—	108–109	48
$C_8H_8N_2O_2$	CH_3	—	—	CH_3	80.9–81.2	14
$C_8H_8N_2O_2$	—	CH_3	CH_3	—	139.4–139.7	14
$C_8H_8N_2O_3$	CH_3	—	OMe	—	105–106	82
$C_8H_8N_2O_3$	—	OEt	—	—	109	57
$C_8H_9N_3O_2$	—	NMe_2	—	—	123–124	27
$C_9H_5N_3O_2$					152	35
$C_9H_5N_3O_2$					184	35
$C_9H_5N_3O_2$	—C_4H_4—[h]		(N)	—	164–165	35

TABLE I—*continued*

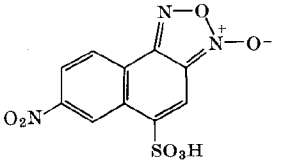
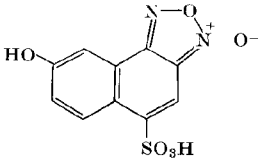
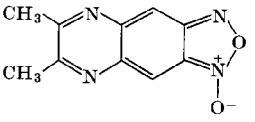
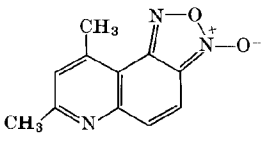
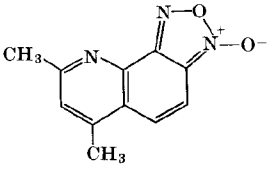
Molecular formula	Substituent at position 4	5	6	7	Melting point (°C)	Ref.
$C_9H_8N_2O_4$	COOEt	—	—	—	108–109	146
$C_9H_9N_3O_4$	—	NHCOOEt	—	—	116–117	27
$C_9H_9ClN_2O_3$	Cl	*i*-PrO	—	—	99.6–100.1	39
$C_9H_{10}N_2O_3$	CH_3	OMe	CH_3	—	96	55
$C_9H_{10}N_2O_5$	OMe	OMe	OMe	—	129.5	23
$C_{10}H_5ClN_2O_2$	—C_4H_4—		Cl	—	140.2–140.8	109
$C_{10}H_5ClN_2O_2$	—C_4H_4—		—	Cl	145.5–146.5	123
$C_{10}H_5ClN_2O_4S$	—C_4H_4—		—	SO_2Cl	221	123
$C_{10}H_5N_3O_4$	—C_4H_4—		NO_2	—	136	144
$C_{10}H_5N_3O_7S$					*e*	111
$C_{10}H_6N_2O_2$	—C_4H_4—		—	—	128–129	6
$C_{10}H_6N_2O_5S$	—C_4H_4—		SO_3H	—	*e*, *i*	109
$C_{10}H_6N_2O_5S$	—C_4H_4—		—	SO_3H	*e*, *i*	123
$C_{10}H_6N_2O_6S$					*e*	112
$C_{10}H_8N_4O_2$					$>300^{g,n}$	85
$C_{10}H_{10}N_2O_2$	—	—$(CH_2)_4$—		—	106–107	18
$C_{10}H_{10}N_4O_5$	NO_2	—	—	$C_4H_8ON^j$	174–175	92
$C_{11}H_8N_2O_2$	—C_4H_4—		CH_3	—	181	35
$C_{11}H_9N_3O_2$					214–215	35
$C_{11}H_9N_3O_2$					240–241	35

TABLE I—*continued*

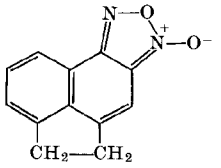
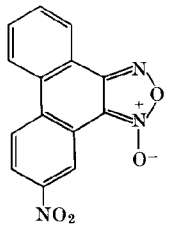
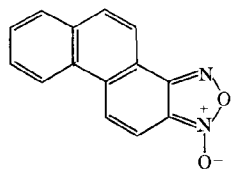
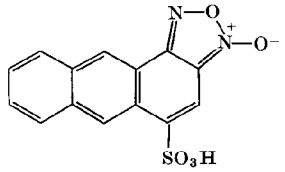
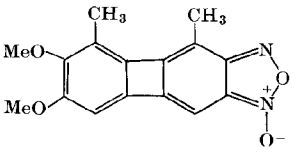
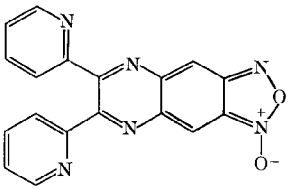
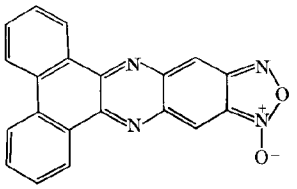
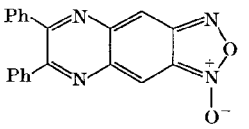
Molecular formula	Substituent at position 4	5	6	7	Melting point (°C)	Ref.
$C_{11}H_{12}N_4O_4$	NO_2	—	—	$C_5H_{10}N$[k]	154–155	92
$C_{11}H_{13}N_3O_4$	—	*t*-BuOCONH	—	—	155–156	27
$C_{12}H_6N_4O_4$	—	Bis[l]	—	—	211	53
$C_{12}H_6N_4O_6S$	—	—SO_2—[m]	—	—	207–209	142
$C_{12}H_7BrN_4O_4$	—	*p*-BrC_6H_4NH	NO_2	—	151	22
$C_{12}H_7ClN_4O_4$	NO_2	—	—	*p*-ClC_6H_4NH	215–216	92
$C_{12}H_7N_3O_4S$	NO_2	—	—	PhS	195–196	92
$C_{12}H_8N_2O_2$					177–178	54
$C_{12}H_8N_4O_4$	NO_2	PhNH	—	—	208–209	92
$C_{12}H_8N_4O_4$	NO_2	—	—	PhNH	150[d]	92
$C_{12}H_8N_4O_4$	—	PhNH	NO_2	—	168	22
$C_{12}H_8N_6O_4$	C_4H_4NO[o]	(N)	(N)	C_4H_4NO	*e*	20
$C_{12}H_9N_3O_4$	Ph	—	NO_2	—	212–213	65
$C_{12}H_{10}N_2O_2$	Ph	—	—	—	87.5–88.5	65
$C_{13}H_8N_2O_4$	—	OCOPh	—	—	137–139	96
$C_{13}H_{10}N_4O_4$	NO_2	—	—	$PhCH_2NH$	169–170	92
$C_{13}H_{10}N_4O_4$	NO_2	—	—	PhNMe	186–187	92
$C_{13}H_{10}N_4O_5$	NO_2	—	—	*p*-$MeOC_6H_4NH$	221–222	92
$C_{14}H_7N_3O_4$					211–212	49
$C_{14}H_8N_2O_2$					221–222	147, 148
$C_{14}H_8N_2O_2$	—C_4H_4—			—C_4H_4—	234–235	79
$C_{14}H_8N_2O_5S$					*e*	76

TABLE I—*continued*

Molecular formula	Substituent at position 4	5	6	7	Melting point (°C)	Ref.
$C_{16}H_8Cl_2N_4O_2$	*p*-ClC_6H_4	(N)	(N)	*p*-ClC_6H_4	235	90
$C_{16}H_8N_6O_6$	*p*-$O_2NC_6H_4$	(N)	(N)	*p*-$O_2NC_6H_4$	252	90
$C_{16}H_8N_6O_6$	*m*-$O_2NC_6H_4$	(N)	(N)	*m*-$O_2NC_6H_4$	251	90
$C_{16}H_{10}N_4O_2$	Ph	(N)	(N)	Ph	210	90
$C_{16}H_{14}N_2O_4$					209–210	149
$C_{18}H_{10}N_6O_2$					*e*, *g*, *n*	85
$C_{18}H_{14}N_4O_4$	*p*-$MeOC_6H_4$	(N)	(N)	*p*-$MeOC_6H_4$	*n*	90
$C_{20}H_{10}N_4O_2$					>300*g*	85
$C_{20}H_{12}N_4O_2$					>300*g*	85
$C_{28}H_{18}N_4O_2$	*p*-PhC_6H_4	(N)	(N)	*p*-PhC_6H_4	*n*	90

[a] Furoxano fused.
[b] ca. 50% D at H(5).
[c] Equilibrium mixture with previous compound.
[d] With decomposition.
[e] Not recorded.
[f] Furazano fused.
[g] Structure doubtful.
[h] Benzo fused.
[i] Isolated as metal salts.
[j] *N*-Morpholino-.
[k] *N*-Piperidino-.
[l] 5,5′-Dibenzofuroxanyl.
[m] Di-(5-benzofuroxanyl) sulfone.
[n] Not obtained pure.
[o] 5-Methylisoxazol-3-yl.

The Indole Grignard Reagents

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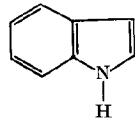
I. Introduction

A decade after Victor Grignard's first publication appeared describing the reagents that bear his name, Oddo reported that indole (**1**),[1,2] like pyrrole,[3] reacted with the simple Grignard reagent, ethylmagnesium iodide, in ether solution to give ethane and indole magnesium iodide.[1,2] The latter compound could be precipitated from ether solution as a pyridine complex.[2]



(**1**)

* *Present Address*: Research Division, Hoffmann-LaRoche, Inc., Nutley, New Jersey.

[1] B. Oddo, *Ber. Deut. Chem. Ges.* **43**, 1012 (1910).
[2] B. Oddo, *Gazz. Chim. Ital.* **41**, 221 (1911); *Chem. Abstr.* **5**, 2638 (1911).
[3] B. Oddo, *Gazz. Chim. Ital.* **39**, 649 (1909); *Chem. Abstr.* **5**, 686 (1911).

The indole Grignard reagents have been widely employed as intermediates in synthetic work, mainly for the introduction of substituents into the 1- or 3-positions of the indole ring system.

The earlier work on the indole Grignard reagents has been reviewed by Oddo[4] and Mingoia.[5,6] Yoffe and Nesmeyanov have listed all the compounds that were prepared by reactions involving Grignard reagents, including those of indole, prior to January 1948.[7] In 1954, two summaries of the chemistry of the indole Grignard reagents were published (Sumpter and Miller[8] and Kharasch and Reinmuth[9]).

In view of the importance of these compounds in indole chemistry and since there is no adequate modern survey of this field, an attempt has been made to review comprehensively the chemistry of the indole Grignard reagents.

The major portion of the current review consists of a discussion of the reactions of the indole magnesium halides, classified according to the chemical nature of the coreactant species. The authors have endeavored to mention all important papers, that describe reactions involving indole Grignard reagents, which have appeared during the past half century. It is hoped that all major publications on the subject that were available before December 31, 1967 have been cited. A short discussion of the ideas that have been advanced to account for the structure and reactivity of the indole Grignard reagent is included at the end of the chapter.

II. Preparation of the Indole Magnesium Halides

The most widely used procedures for the preparation of the indole magnesium halides are based on the method originally described by Oddo in 1911,[2] and consist of adding a solution of indole or an indole derivative, in dry diethyl ether, to a solution of an alkyl magnesium

[4] B. Oddo, *Mem. Reale Accad. Nazl. Lincei, Classe Sci. Fis. Mat. Nat.* **14**, 510 (1923); *Chem. Abstr.* **19**, 2492 (1925).

[5] Q. Mingoia, *Rev. Brasil. Chim.* (*Sao Paulo*) **4**, 183 (1937); *Chem. Abstr.* **32**, 549 (1938).

[6] Q. Mingoia, *Boll. Chim. Farm.* **77**, 337 (1938); *Chem. Abstr.* **32**, 7035 (1938).

[7] S. T. Yoffe and A. N. Nesmeyanov, "Handbook of Magnesium Organic Compounds," Vols. I, II, & III. Pergamon, Oxford, 1956.

[8] W. C. Sumpter and F. M. Miller, "Heterocyclic Compounds with Indole and Carbazole Systems," p. 50. Wiley (Interscience), New York, 1954.

M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances." Prentice-Hall, Englewood Cliffs, New Jersey, 1954.

halide, usually ethyl(or methyl)magnesium iodide(or bromide) in ether. There is, however, a considerable variation in the reported temperatures and times required to complete the reaction, but it was usually assumed that quantitative conversion of the indole to the indole Grignard reagent had occurred.

Anisole and mixtures of diethyl ether with aromatic hydrocarbons have both been widely employed as solvents for these reactions.[10–13] Ethers other than diethyl ether and anisole have also been successfully used (cf. refs. 14–17). Hexamethylphosphorotriamide has recently been used as a solvent for indole Grignard reactions.[18,19] Young and Mizianty have recently described the use of an aromatic magnesium halide (phenylmagnesium bromide) for the synthesis of indole magnesium bromide.[20–22]

Oddo reported that the organomagnesium derivatives of pyrrole, indole, skatole, and carbazole could be prepared in a single operation by mixing the parent heterocyclic compound with an alkyl halide and magnesium in anhydrous ether.[23] The product formed was reported to be the same as that obtained by the more conventional procedure. However, this approach to the synthesis of the indole Grignard reagents does not seem to have been exploited in subsequent work.

An example of the formation of a Grignard reagent on the benzene ring moiety of the indole nucleus has been described recently. Noland

[10] R. Majima and M. Kotake, *Ber. Deut. Chem. Ges.* **55B**, 3859 (1922).

[11] R. Majima and M. Kotake, *Ber. Deut. Chem. Ges.* **55B**, 3865 (1922).

[12] N. Putochin, *Ber. Deut. Chem. Ges.* **59B**, 1987 (1926).

[13] N. Putochin, *Zh. Russ. Fiz. Chem. Obshchestva* **59**, 761 (1927); *Chem. Abstr.* **22**, 3409 (1928).

[14] G. F. Smith and A. E. Walters, *J. Chem. Soc.* p. 940 (1961).

[15] M. G. Reinecke, H. W. Johnson, and J. F. Sebastian, *Tetrahedron Letters*, p. 1183 (1963).

[16] C. R. Ganellin and H. F. Ridley, personal communication, 1967.

[16a] H. F. Ridley, Ph.D. Thesis, University of London, May 1966.

[16b] C. R. Ganellin, D. R. Hollyman, and H. F. Ridley, *J. Chem. Soc.* p. 2220 (1967).

[17] J. C. Powers, W. P. Meyer, and T. G. Parsons, *J. Am. Chem. Soc.* **89**, 5812 (1967).

[18] G. Casnati and A. Pochini, *Chim. Ind.* (*Milan*) **48**, 262 (1966).

[19] B. Cardillo, G. Casnati, and A. Pochini, *Chim. Ind.* (*Milan*) **49**, 172 (1967).

[20] T. E. Young, *J. Org. Chem.* **27**, 507 (1962).

[21] T. E. Young and M. F. Mizianty, *J. Org. Chem.* **29**, 2030 (1964).

[22] T. E. Young and M. F. Mizianty, *J. Med. Chem.* **9**, 635 (1966).

[23] B. Oddo, *Gazz. Chim. Ital.* **44**, 482 (1914); *Chem. Abstr.* **8**, 3019 (1914).

and Reich obtained a Grignard reagent from 5-bromo-1,3-dimethylindole which appeared to behave normally on oxidation or carbonation.[24]

III. Reactions of the Indole Magnesium Halides

A. General Comments

In some instances the reactions of the indole Grignard reagents resemble those of simple aryl or alkyl magnesium halides, but in many cases they appear to react anomalously.

A wide variety of reaction temperatures and times have been employed in carrying out these reactions; in an extreme case temteratures of up to ca. 350° were employed. Under these conditions it is quite possible that the actual products isolated were formed as the result of secondary reactions occurring after the primary products had been formed. Standard procedures for the working up of reaction mixtures obtained in Grignard reactions are usually followed.

The structures of the products formed were often ascertained by chemical procedures, which could have led to erroneous conclusions, e.g., the position of the substituent which had been introduced into the indole ring system was sometimes determined by identification of the indole carboxylic acid obtained on alkali fusion. Active hydrogen determinations by the Zerewitinov method and silver derivative formation were two methods widely used for establishing the presence or absence of a substituent on the indole nitrogen atom; both these procedures could possibly have given misleading results. More recently, however, less ambiguous physical methods of structural determination, such as infrared and nuclear magnetic resonance spectroscopy, have been extensively employed.

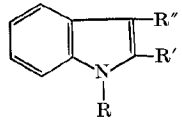
B. Reactions with Organic Halogen Compounds

1. *Alkyl Halides*

Oddo[1,2] reported over 50 years ago that the interaction of methyl iodide with indole magnesium iodide at the reflux temperature of ether for 12 hours produced 3-methylindole (**2**). Rather surprisingly,

[24] W. E. Noland and C. Reich, *J. Org. Chem.* **32**, 828 (1967).

he stated that 1-methylindole (**3**) and 1,3-dimethylindole (**4**) were obtained when the reaction was carried out under similar conditions but for a shorter time. However, under more vigorous conditions (i.e., heating for 15 hours, in the presence of anhydrous potassium chloride) **2** was definitely obtained.[2] 3-Ethylindole (**5**) was formed more readily than the methyl derivative by the action of ethyl iodide on indole magnesium iodide.[2] More recently, however, Sebastian reported that **2** was essentially the only product obtained in significant amounts by the action of methyl iodide on the indole Grignard reagent when the reaction was carried out in tetrahydrofuran at 23°.[25] A number of other alkyl indoles, including: 3-ethyl-2-methylindole (**6**),[26] 3-ethyl-2-*n*-propylindole (**7**),[26] 3-*n*-butylindole (**8**),[16, 16a, 16b] 3-*tert*-butylindole (**9**),[14] 3-isoamylindole (**10**),[19] and 3-*sec*-octylindole (**11**)[27] have also been prepared by the action of the appropriate alkyl halides on the indole Grignard reagent in question. The reaction of indole magnesium bromide with isoamyl bromide has recently been studied in some detail; it was observed that the reaction was inhibited by increasing the basicity of the solvent and that the use of certain solvents, such as hexamethylphosphorotriamide, resulted in essentially exclusive 1-alkylation occurring[19] (cf. Section IV).

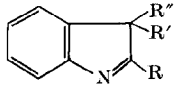


(**2**) R = R′ = H; R″ = CH_3
(**3**) R = CH_3; R′ = R″ = H
(**4**) R = R″ = CH_3; R′ = H
(**5**) R = R′ = H; R″ = C_2H_5
(**6**) R = H; R′ = CH_3; R″ = C_2H_5
(**7**) R = H; R′ = *n*-C_3H_7; R″ = C_2H_5
(**8**) R = R′ = H; R″ = *n*-C_4H_9
(**9**) R = R′ = H; R″ = *tert*-C_4H_9
(**10**) R = R′ = H; R″ = iso-C_5H_{11}
(**11**) R = R′ = H; R″ = *sec*-C_8H_{17}

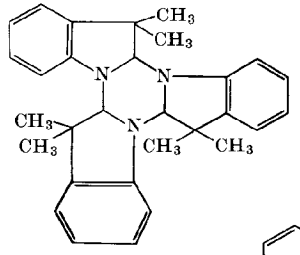
Hoshino reported that a product, described as 3,3-dimethylindolenine (**12**), accompanied by some 1,3-dimethylindole (**4**) and a

[25] J. F. Sebastian, Ph.D. Thesis, University of California, Riverside, 1965.
[26] P. L. Julian and J. Pikl, *Proc. Indiana Acad. Sci.* **45**, 145 (1935); *Chem. Abstr.* **31**, 1026 (1937).
[27] A. H. Jackson and P. Smith, *Tetrahedron*, **24**, 2227 (1968).

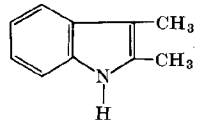
small quantity of an unidentified compound, was obtained by treating skatole magnesium iodide with methyl iodide in benzene at 80°.[28–30] Recently Jackson and Smith[31] have pointed out that several different melting points (i.e., 170°–172°,[32] 152°,[33] and 214°[30,33]) for 3,3-dimethylindolenine (**12**) have been reported. Hoshino reported that the melting point of the compound described as 3,3-dimethylindolenine (**12**) was initially 185°–186°, but this changed to 160°–210° on recrystallization; the change in melting point was accompanied by an apparent increase in molecular weight by a factor of three. However,



(**12**) R = H; R′ = R″ = CH_3
(**15**) R = R′ = R″ = CH_3
(**16**) R = R′ = CH_3; R″ = iso-C_3H_7
(**17**) R = R′ = CH_3; R″ = *tert*-C_4H_9
(**18**) R = H; R′ = R″ = C_2H_5
(**19**) R = H; R′ = CH_3; R″ = C_2H_5
(**20**) R = H; R′ = CH_3; R″ = iso-C_3H_7
(**21**) R = H; R′ = CH_3; R″ = $CH_2C_6H_5$



(**13**)



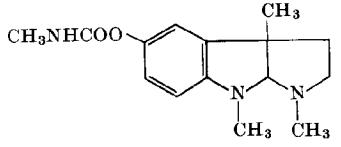
(**14**)

Hoshino further reported that both the melting point and apparent molecular weight of **12** decreased on storage.[28–30] Jackson and Smith, although agreeing that the product in question was 3,3-dimethylindolenine (**12**), reported that the melting point of a purified sample of **12** increased on storage from 172°–176° to more than 200° in 1 week. These authors suggested that polymerization of the monomeric indolenine **12** to the trimeric form **13** was responsible for this and offered spectroscopic evidence to support their contention.[31] Fritz

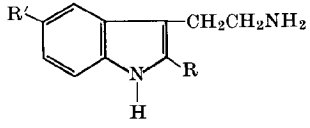
[28] T. Hoshino, *Proc. Imp. Acad. (Tokyo)* **8**, 171 (1932); *Chem. Abstr.* **26**, 4814 (1932).
[29] T. Hoshino, *Abstr. Japan. Chem. Lit.* **6**, 390 (1932); *Chem. Abstr.* **27**, 291 (1933).
[30] T. Hoshino, *Ann. Chem.* **500**, 35 (1933).
[31] A. H. Jackson and A. E. Smith, *Tetrahedron* **21**, 989 (1965).
[32] K. Brunner, *Monatsh. Chem.* **16**, 850 (1895).
[33] R. Robinson and H. Suginome, *J. Chem. Soc.* p. 298 (1932).

and Pfaender recently also reported NMR evidence which shows that **12** exists completely as the monomer at temperatures above 120°, whereas at low temperatures it exists in the trimeric form **13**.[34]

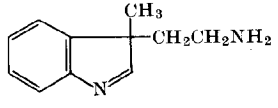
2,3-Dimethylindole (**14**) and 2,3,3-trimethylindolenine (**15**) were obtained by the action of methyl iodide on 2-methylindole magnesium iodide.[28–30] The trisubstituted indolenine derivative **15** was also formed in good yield in a similar manner from 2,3-dimethylindole magnesium iodide.[28–30] Nakazaki and his co-workers have described the preparation of a number of 2,3,3-trisubstituted indolenines,[35,36] including 2,3,3-trimethylindolenine (**15**), 2,3-dimethyl-3-isopropylindolenine (**16**), and 2,3-dimethyl-3-*tert*-butylindolenine (**17**) by Hoshino's procedure (cf. ref. 30). The synthesis of a number of new 3,3-dialkylindolenines, including 3,3-diethylindolenine (**18**), 3-ethyl-3-methylindolenine (**19**), 3-isopropyl-3-methylindolenine (**20**), and 3-benzyl-3-methylindolenine (**21**) by alkylation of the Grignard derivatives of the appropriate 3-alkylindole has recently been described.[27]



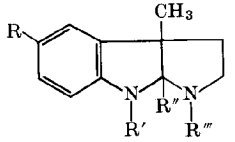
(**22**)



(**23**) R = R′ = H
(**27**) R = CH_3; R′ = H
(**29**) R = H; R′ = OC_2H_5



(**24**)



(**25**) R = R′ = R″ = R‴ = H
(**26**) R = R′ = R‴ = H; R″ = CH_3
(**28**) R = OC_2H_5; R′ = R″ = R‴ = H
(**30**) R = OC_2H_5; R′ = R‴ = CH_3; R″ = H
(**31**) R = OC_2H_5; R′ = R″ = H; R‴ = CH_3

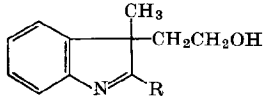
[34] H. Fritz and P. Pfaender, *Chem. Ber.* **98**, 989 (1965).
[35] M. Nakazaki, S. Isoe, and K. Tanno, *Nippon Kagaku Zasshi* **76**, 1262 (1955); *Chem. Abstr.* **51**, 17878 (1957).
[36] M. Nakazaki, *Bull. Chem. Soc. Japan* **32**, 838 (1959); *Chem. Abstr.* **54**, 13096 (1960).

A number of synthetic approaches to the pyrrolo[2,3-*b*]indole ring system, present in the physostigmine [i.e., eserine (**22**)] molecule, which involve indole Grignard reagents as intermediates, have been described.

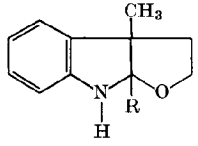
Hoshino and his co-workers reported that treatment of the Grignard reagent obtained from tryptamine (**23**), by the action of a suitable alkyl magnesium halide, with methyl iodide in benzene did not give the expected indolenine derivative **24**; instead dinordeoxyeseroline (**25**) was obtained.[28–30, 37]

Dinordeoxy-9-methyleseroline (**26**) was similarly obtained in high yield, from 2-methyltryptamine (**27**).[28–30, 37] Hoshino and his colleagues obtained dinoreserethole (**28**) by the action of methyl iodide on the Grignard reagent derived from 5-ethoxytryptamine (**29**) in anisole after heating the reaction mixture at 100° for 2 hours.[38, 39] *dl*-Eserethole (**30**) was finally obtained by the methylation of isonoreserethole (**31**), obtained by methylation of the 3-(β-methylaminoethyl)-5-ethoxyindole Grignard reagent with methyl iodide.[38, 40]

Hoshino and Shimodaira observed that the interaction of methyl iodide with the tryptophol Grignard reagent in anisole gave a product, expected to be 3-methyl-3-(β-hydroxyethyl)indolenine (**32**).[41, 42] The relatively weak basic strength of this product was, however, incompatible with an indolenine structure; consequently **32** should probably be formulated in the fully cyclized form (i.e., **33**).[41, 42] Nakazaki has recently shown that the Grignard reagent derived from 2-methyltryptophol undergoes an analogous reaction with methyl iodide; the



(**32**) R = H
(**35**) R = CH_3



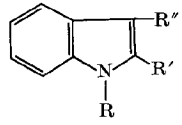
(**33**) R = H
(**34**) R = CH_3

[37] T. Hoshino and K. Tamura, *Ann. Chem.* **500**, 42 (1933).
[38] T. Hoshino and T. Kobayashi, *Ann. Chem.* **516**, 81 (1935).
[39] T. Hoshino and Y. Kotake, *Ann. Chem.* **516**, 76 (1935).
[40] T. Hoshino and T. Kobayashi, *Ann. Chem.* **520**, 11 (1935).
[41] T. Hoshino, *Proc. Imp. Acad. (Tokyo)* **10**, 159 (1934); *Chem. Abstr.* **28**, 5439 (1934).
[42] T. Hoshino and K. Shimodaira, *Ann. Chem.* **520**, 19 (1935).

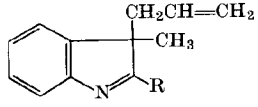
final product in this case being 3*a*,8*a*-dihydro-3*a*,8*a*-dimethyl-3*H*-furo[2,3-*b*]indole (**34**),[43] presumably formed by cyclization of the intermediate indolenine derivative **35**.[43]

2. *Alkenyl Halides*

It is only in relatively recent years that the interaction of indole Grignard reagents with unsaturated aliphatic halogen compounds has



(**36**) R = R′ = H; R″ = $CH_2CH{=}CH_2$
(**38**) R = $CH_2CH{=}CH_2$; R′ = H; R″ = CH_3
(**39**) R = H; R′ = $CH_2CH{=}CH_2$; R″ = CH_3
(**40**) R = $CH_2CH_2CH_3$; R′ = H; R″ = CH_3
(**41**) R = H; R′ = $CH_2CH_2CH_3$; R″ = CH_3
(**43**) R = H; R′ = CH_3; R″ = $CH_2CH_2CH_3$
(**44**) R = H; R′ = CH_3; R″ = $CH_2CH{=}CH_2$
(**45**) R = $CH_2CH_2CH_2CH_3$; R′ = H; R″ = CH_3
(**46**) R = H; R′ = $CH_2CH_2CH_2CH_3$; R″ = CH_3
(**47**) R = $CH_2CH_2CH(CH_3)_2$; R′ = H; R″ = CH_3
(**48**) R = H; R′ = $CH_2CH_2CH(CH_3)_2$; R″ = CH_3



(**37**) R = H
(**42**) R = CH_3

been studied. 3-Allylindole (**36**) has been obtained by the action of allyl bromide on indole magnesium halides.[18, 19, 44–46] Using hexamethylphosphorotriamide as solvent Cardillo *et al.* obtained essentially only 1-allylindole in this reaction.[19] Jackson and Smith reported that the skatole Grignard reagent reacted with allyl bromide at 0° in

[43] M. Nakazaki, *Bull. Chem. Soc. Japan* **32**, 588 (1959); *Chem. Abstr.* **54**, 7686 (1960).
[44] J. B. Brown, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.* p. 3172 (1952).
[45] M. Nakazaki and S. Isoe, *Nippon Kagaku Zasshi* **76**, 1159 (1955); *Chem. Abstr.* **51**, 17877 (1957).
[46] N. Lerner, *Dissertation Abstr.* **24**, 4982 (1964).

benzene–ether solution to give mainly 3-allyl-3-methylindolenine (**37**), accompanied by a mixture of 1-allyl-3-methylindole (**38**) and 2-allyl-3-methylindole (**39**).[31] 1-Allyl-3-methylindole (**38**) and 2-allyl-3-methylindole (**39**), both relatively unstable compounds, were isolated as the corresponding *n*-propyl derivatives **40** and **41** after hydrogenation. The structures of **40** and **41** were confirmed spectroscopically and by alternate syntheses.[31] Nakazaki prepared 3-allyl-2,3-dimethylindolenine (**42**) by the allylation of 2,3-dimethylindole magnesium bromide with allyl bromide in ether.[36]

3-Allyl-3-methylindolenine (**37**) was also synthesized by the action of methyl iodide on 3-allylindole magnesium iodide; however, the yield of **37** was not as good as that obtained in the procedure starting from 3-methylindole.[31]

2-Methyl-3-*n*-propylindole (**43**) was obtained by hydrogenation of the intermediate 2-methyl-3-allylindole (**44**), obtained by the allylation of 2-methylindole magnesium iodide. There were no reports of isomeric products being formed in this reaction.[31]

Jackson and Smith further showed that crotyl bromide reacts with 3-methylindole magnesium iodide to give a mixture of products from which 1-*n*-butyl-3-methylindole (**45**) and 2-*n*-butyl-3-methylindole (**46**) could be isolated after hydrogenation. 3-Methyl-1-isopentylindole (**47**) and 3-methyl-2-isopentylindole (**48**) were similarly obtained by hydrogenation of the initial products obtained when the indole Grignard reagent was allowed to react with 3,3-dimethylallyl bromide in the first instance.[31]

3. *Alkynyl Halides*

Brown *et al.* were not able to prepare 3-(prop-2-ynyl)indole [i.e., 3-propargylindole (**49**)] by the Grignard reaction[44]; however, Williamson[47] and later Zenitz[48] readily obtained **49** in satisfactory yield by the action of propargyl bromide on indole magnesium bromide in anisole.

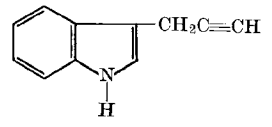
4. *Arylalkyl Halides*

a. *Benzyl Chloride.* In the early 1930's Hoshino showed that 3-benzyl-2-methylindole (**50**) and 3,3-dibenzyl-2-methylindolenine

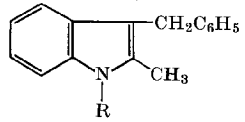
[47] W. R. N. Williamson, *J. Chem. Soc.* p. 2834 (1962).

[48] B. L. Zenitz, U.S. Patent No. 3,238,215 (1966); *Chem. Abstr.* **65**, 7145 (1966).

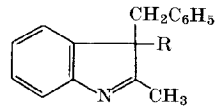
(**51**) were obtained by the action of benzyl chloride on the magnesium derivative of 2-methylindole.[28–30] The indolenine **51** was also produced by the action of benzyl chloride on the 3-benzyl-2-methylindole (**50**) Grignard reagent; in this case some 1,3-dibenzyl-2-methylindole (**52**) was formed as a by-product.[28–30] More recently Nakazaki and his co-workers used essentially Hoshino's procedure for the synthesis of 3-benzyl-2,3-dimethylindolenine (**53**).[35, 36]



(**49**)



(**50**) R = H
(**52**) R = $CH_2C_6H_5$



(**51**) R = $CH_2C_6H_5$
(**53**) R = CH_3

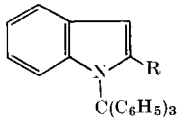
b. *Triphenylmethyl Chloride.* In 1936 Funakubo and Hirotani claimed that 1-triphenylmethylindole (**54**) and 2-methyl-1-triphenylmethylindole (**55**) were obtained when the reaction between triphenylmethyl chloride and indole or 2-methylindole magnesium iodide, respectively, was carried out at the reflux temperature of ether.[49] Two years later Kubota reported the results of an extensive study of the products obtained by the interaction of triphenylmethyl chloride with the Grignard reagents derived from indole and a number of 2-substituted indoles in anisole[50] and concluded that, in contrast to the earlier findings,[49] the products were 3-substituted indoles (cf. ref. 51). In this manner Kubota obtained 3-triphenylmethylindole (**56**), 2-methyl-3-triphenylmethylindole (**57**), 2-phenyl-3-triphenylmethylindole (**58**), 2-(α-naphthyl)-3-triphenylmethylindole (**59**), and 2-(β-naphthyl)-3-triphenylmethylindole (**60**) by the action of triphenylmethyl chloride on the Grignard reagents derived from indole (**1**), 2-methylindole (**61**), 2-phenylindole (**62**), 2-(α-naphthyl)indole (**63**),

[49] E. Funakubo and T. Hirotani, *Ber. Deut. Chem. Ges.* **69B**, 2123 (1936).

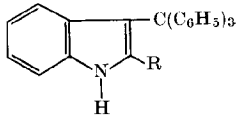
[50] T. Kubota, *Nippon Kagaku Zasshi*, **59**, 399 (1938); *Chem. Abstr.* **32**, 9080 (1938).

[51] It is reported incorrectly in one recent review article (cf. ref. 8) that these products are 2-substituted indoles.

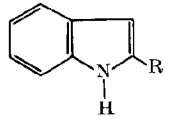
and 2-(β-naphthyl)indole (**64**), respectively.[50] The triphenylmethylindoles **56**, **57**, **58**, **59**, and **60** were formulated a 3-substituted indoles since they all apparently contained one active hydrogen atom and it was assumed that this was in the 1-position. 2,3-Diphenylindole magnesium iodide also reacted with triphenylmethyl chloride in anisole solution; in this case 2,3-diphenyl-3-triphenylmethylindolenine (**65**) was obtained. Kubota observed also that the Grignard reagents derived from the benz[*e*]indoles (**66**) and (**67**) reacted with triphenylmethyl chloride to give the expected 3-triphenylmethyl derivatives;



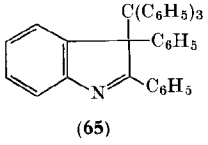
(**54**) R = H
(**55**) R = CH_3



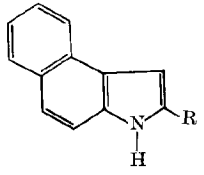
(**56**) R = H
(**57**) R = CH_3
(**58**) R = C_6H_5
(**59**) R = α-naphthyl
(**60**) R = β-naphthyl



(**61**) R = CH_3
(**62**) R = C_6H_5
(**63**) R = α-naphthyl
(**64**) R = β-naphthyl



(**65**)

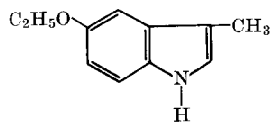


(**66**) R = H
(**67**) R = CH_3
(**68**) R = C_6H_5

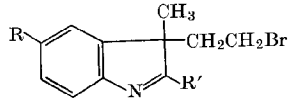
however, no reaction occurred between 2-phenylbenz[4,5]indole (**68**) and triphenylmethyl chloride.[50] In all cases the position of the trityl group was established by the fact that the compounds appeared to contain one active hydrogen atom as determined by the Zerewitinov procedure. Since the hydrogen atom in the 3-position in indole derivatives of this type might also react positively in the Zerewitinov reaction, a completely unambiguous structural evaluation must await further investigation.

5. *Aliphatic Polyhalides*

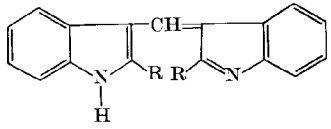
a. 1,2-*Dibromoethane.* In 1939, Kobayashi extended his synthetic approaches to the eserine skeleton to a study of the interaction of 1,2-dibromoethane with the Grignard reagents derived from 3-methylindole (**2**), 2,3-dimethylindole (**14**), and 5-ethoxy-3-methylindole (**69**).[52] In all cases the initial product was probably a 3-(2-bromoethyl)-3-methylindolenine derivative [i.e., **70**, **71**, and **72**, respectively]. The crude products were cyclized by treatment with ammonia at 100°–105° in a sealed tube, giving dinordeoxyeseroline (**25**), dinordeoxy-9-methyleseroline (**26**) and dinoreserethole (**28**), respectively.[52]



(**69**)



(**70**) R = R′ = H
(**71**) R = H; R′ = CH_3
(**72**) R = OC_2H_5; R′ = H



(**73**) R = CH_3
(**74**) R = H

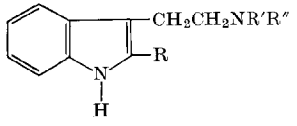
b. *Iodoform and Carbon Tetrachloride.* Iodoform reacts slowly with 2-methylindole magnesium bromide in anhydrous ether to form an orange-yellow solid, probably 2-methyl-3-indolyl-2′-methyl-3′-indoleninylidenemethane (**73**).[53] The same product was obtained by the action of carbon tetrachloride on 2-methylindole magnesium iodide.[54] The related compound, 3-indolyl-3′-indoleninylidenemethane (**74**) was obtained analogously from indole magnesium bromide.[54]

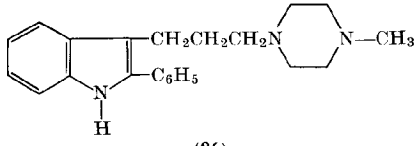
[52] T. Kobayashi, *Ann. Chem.* **539**, 213 (1939).
[53] B. Oddo and F. Tognaschini, *Gazz. Chim. Ital.* **53**, 271 (1923); *Chem. Abstr.* **17**, 2883 (1923).
[54] B. Oddo and G. Sanna, *Gazz. Chim. Ital.* **54**, 682 (1924); *Chem. Abstr.* **19**, 829 (1925).

6. *Miscellaneous Alkyl Halide Derivatives*

a. *Ethylene Chlorohydrin.* An early attempt to prepare tryptophol by the action of ethylene chlorohydrin on the indole Grignard reagent was not very successful.[42] However, tryptophol can be readily prepared from the indole Grignard reagent by reaction with ethylene oxide (see Section III,F,1,a).

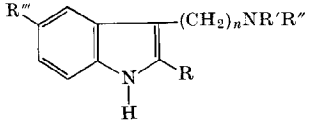
b. *Halogenoalkylamine Derivatives.* The preparation of 3-(β-diethylaminoethyl)-2-methylindole (**75**) by the action of β-diethylaminoethyl chloride on 2-methylindole magnesium bromide in ether solution was first described in 1931.[55] In 1964, Ganellin and Ridley reported that N^{ω},N^{ω}-dimethyltryptamine (**76**), 2,N^{ω},N^{ω}-trimethyltryptamine (**77**),





(**86**)

(**75**) R = CH_3; R′ = R″ = C_2H_5
(**76**) R = H; R′ = R″ = CH_3
(**77**) R = R′ = R″ = CH_3
(**78**) R = C_6H_5; R′ = R″ = CH_3



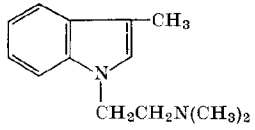
(**79**) R = H; R′ = H; R″ = CH_3; R‴ = H; $n = 2$
(**80**) R = C_6H_5; R′ = CH_3; R″ = CH_3; R‴ = F; $n = 2$
(**81**) R = C_6H_5; R′ = CH_3; R″ = CH_3; R‴ = OCH_3; $n = 2$
(**82**) R = 4-FC_6H_4; R′ = CH_3; R″ = CH_3; R‴ = H; $n = 2$
(**83**) R = C_6H_5; R′ = CH_3; R″ = CH_3; R‴ = H; $n = 3$
(**84**) R = $CH_2C_6H_5$; R′ = CH_3; R″ = CH_3; R‴ = H; $n = 2$
(**85**) R = H; R′ = C_2H_5; R″ = C_2H_5; R‴ = H; $n = 2$

and N^{ω},N^{ω}-dimethyl-2-phenyltryptamine (**78**) were obtained in reasonable yield by the action of β-dimethylaminoethyl chloride on the Grignard reagents derived from indole, 2-methylindole, and 2-phenylindole, respectively, in anisole solution, at low temperatures.[56] The yields of **76**, **77**, and **78** were adversely affected by raising

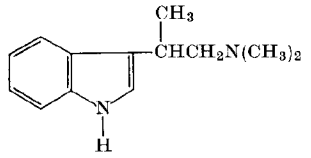
[55] J. Klarer and F. Mietzsch, U.S. Patent, 1,793,176 (1931); *Chem. Abstr.* **25**, 2153 (1931).
[56] C. R. Ganellin and H. F. Ridley, *Chem. Ind.* (*London*) p. 1388 (1964).

the reaction temperature and none of the desired product was obtained when the reaction was carried out in diethyl ether, tetrahydrofuran,[56] or benzene.[16, 16a, 16b, 56]

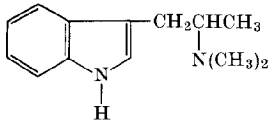
Ganellin and Ridley subsequently showed that this reaction was of wide applicability and could be applied to the synthesis of tryptamine (**23**) itself and a number of indole derivatives with 3-β-mono- or 3-β-dialkylaminoalkyl side chains where the side chain contained two or more carbon atoms.[16, 16a, 16b] A number of compounds of this general type including **79**, **80**, **81**, **82**, **83**, **84**, **85**, and **86** have been prepared by these authors.[16, 16a, 16b] Trace quantities of the corresponding 1-(β-dialkylaminoethyl)indole derivatives were formed at the same time as other isomers. However, only the *N*-substituted product,



(**87**)



(**88**)



(**89**)

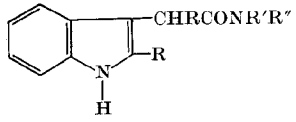
i.e., 1-(2-dimethylaminoethyl)-3-methylindole (**87**) was obtained from the skatole Grignard reagent. Attempts to replace the chlorodialkylamino component by the corresponding bromo compounds in the coupling reaction were not encouraging.[16, 16a, 16b] Kalir and Szara obtained an 8% yield of dimethyltryptamine (**76**) by the action of dimethylaminoethyl chloride, or mesylate, on indole magnesium bromide; however, only traces of the corresponding tryptamine derivatives were obtained using either the diethyl- or diisopropylaminoethyl chlorides.[57]

Ganellin and Ridley obtained a mixture of isomeric products by the action of 2-chloro-1-dimethylaminopropane on indole magnesium iodide. In this case both 3-(2-dimethylamino-1-methylethyl)

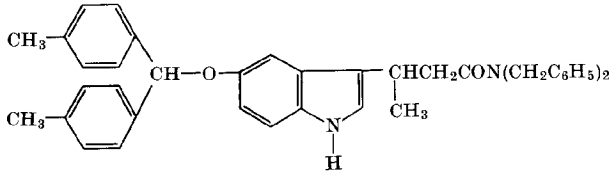
[57] A. Kalir and S. Szara, *J. Med. Chem.* **9**, 341 (1966).

indole (**88**) and 3-(β-dimethylamino-*n*-propyl)indole (**89**) were formed.[16, 16a, 16b] Eiter and Svierak had reported earlier that they were unable to alkylate indole magnesium iodide with 1-chloro-2-dimethylaminopropane in ether.[58]

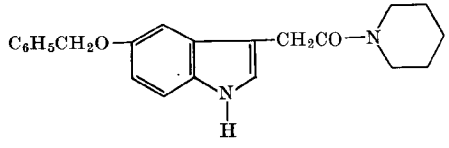
c. *α-Chloro-N-substituted Acetamides.* In 1937 Wegler and Binder reported that *N*,*N*-diethyl-3-indolylacetamide (**90**) could be obtained



(**90**) R = R′ = H; R″ = R‴ = C_2H_5
(**91**) R = H; R′ = R″ = R‴ = CH_3



(**92**)



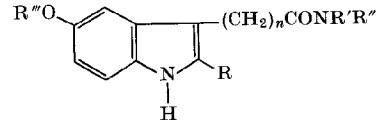
(**93**)

by the action of *N*,*N*-diethyl-α-chloroacetamide on indole magnesium iodide.[59] This reaction has subsequently been shown to be of general utility and a number of substituted 3-indolylacetamides including **91**, **92**, **93**, and the compounds listed in Table I (i.e., **94–102**) have been made by this route.[16, 16a, 16b, 60, 61] The reaction is carried out by heating the chloro compound and the Grignard reagent together in the

[58] K. Eiter and O. Svierak, *Monatsh. Chem.* **83**, 1453 (1952).
[59] R. Wegler and H. Binder, *Arch. Pharm.* **275**, 506 (1937); *Chem. Abstr.* **32**, 939 (1938).
[60] M. E. Speeter, U.S. Patent No. 2,692,882 (1954); *Chem. Abstr.* **49**, 14810 (1955).
[61] R. V. Heinzelman and J. Szmuszkovicz, *Progr. Drug Res.* **6**, 75 (1963).

absence of solvent for several hours. The method was reported to be most successful with disubstituted amides, less successful with monosubstituted amides, and it failed completely with chloroacetamide itself (cf. ref. 61).

TABLE I

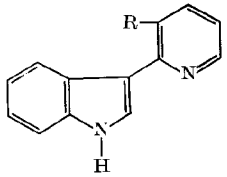


Compound number	R	R′	R″	R‴	*n*
94	H	CH_3	$C_6H_5CH_2$	$C_6H_5CH_2$	1
95	H	$C_6H_5CH_2$	$C_6H_5CH_2$	$C_6H_5CH_2$	1
96	H	H	$C_6H_5CH_2$	$C_6H_5CH_2$	1
97	CH_3	H	CH_3	$C_6H_5CH_2$	1
98	H	$C_6H_5CH_2$	$C_6H_5CH_2$	*p*-$CH_3OC_6H_4$ >CH *p*-$CH_3OC_6H_4$	2
99	H	H	$C_6H_5CH_2$	$(C_6H_5)_2CH$	1
100	C_2H_5	CH_3	$C_6H_5CH_2$	*p*-ClC_6H_4 >CH *p*-ClC_6H_4	1
101	H	$(CH_3)_2CH$	$C_6H_5CH_2$	$C_6H_5CH_2$	1
102	H	C_2H_5	C_2H_5	$C_6H_5CH_2$	2

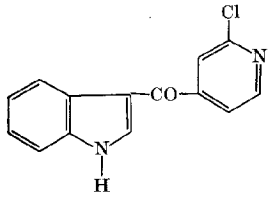
7. *Heterocyclic Halogen Compounds*

Powers reported recently that 3-(2-pyridyl)indole (**103**) is obtained in ca. 17% yield by the interaction of 2-chloropyridine with indole magnesium iodide in a sealed tube at 160° for 12 hours.[62] 3-(3-Cyano-2-pyridyl)indole (**104**) was obtained in 52% yield when the indole Grignard reagent was heated with 2-chloro-3-cyanopyridine at 170° for 3 hours. However, 2-chloro-4-cyanopyridine reacted in a somewhat different manner under similarly vigorous conditions; in this case 3-indolyl 2-chloro-4-pyridyl ketone (**105**) was obtained. This product

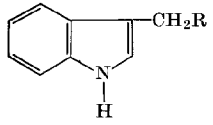
[62] J. C. Powers, *J. Org. Chem.* **30**, 2534 (1965).



(**103**) R = H
(**104**) R = CN



(**105**)



(**106**) R = 2-Pyridyl
(**107**) R = 3-Pyridyl
(**108**) R = 4-Pyridyl

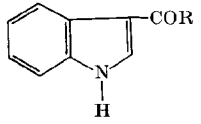
was presumably formed by the initial addition of the Grignard reagent to the nitrile group. The structure of **105** was confirmed by an alternative synthesis.[62]

2-(3-Indolylmethyl)pyridine (**106**), 3-(3-indolylmethyl)pyridine (**107**), and 4-(3-indolylmethyl)pyridine (**108**) have recently been prepared by the condensation of indole magnesium bromide with 2-, 3-, and 4-chloromethylpyridine, respectively.[63]

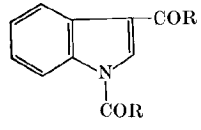
C. Reactions with Derivatives of Organic Acids

1. *Aliphatic Monocarboxylic Acid Chlorides*

a. *Unsubstituted.* In 1911 Oddo and Sessa reported that 3-acetylindole (**109**) was formed readily in a vigorous reaction between indole



(**109**) R = CH_3
(**111**) R = C_2H_5
(**113**) R = n-C_3H_7



(**110**) R = CH_3
(**112**) R = C_2H_5
(**114**) R = n-C_3H_7

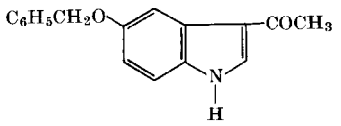
[63] J. I. DeGraw, J. G. Kennedy, and W. A. Skinner, *J. Heterocyclic Chem.* **3**, 67 (1966).

magnesium iodide and acetyl chloride in ether and that small quantities of the disubstituted product, 1,3-diacetylindole (**110**), were also formed. 3-Propionylindole (**111**) and 1,3-dipropionylindole (**112**) were obtained similarly from propionyl chloride and indole magnesium iodide. These authors concluded that the amount of diacyl derivative formed decreased with the complexity of the acid chloride used. When the reaction was carried out with n-butyryl chloride they were able to detect only the 3-acyl derivative (**113**).[64] However, more recently Hishida has obtained both 3-n-butyrylindole (**113**) and 1,3-di(n-butyryl)indole (**114**) by the action of n-butyryl chloride on the indole Grignard reagent, the formation of **114** being favored by low reaction temperatures.[65] In 1922 Majima and Kotake reported the effect of varying the solvent on the yield of 3-acetylindole (**109**), obtained by the action of acetyl chloride on indole magnesium iodide; a 93% yield of **109** was obtained when the reaction was carried out in ether in the cold; however, only a 61% yield was obtained in anisole. They did not, however, report the formation of any of the 1,3-diacetyl derivative **110**.[11] Baker in 1946 also obtained **109** as the main product by this route, when the reaction was carried out at $-20°$ in ether; small quantities of **110** were formed at the same time.[66] In 1952 Saxton reported that good yields of **109** could not be consistently obtained by this procedure.[67] However, more recently Szmuskovicz claimed that the original Grignard procedure for the preparation of **109** was improved if the reaction with the acid chloride was carried out in benzene solution. Szmuskovicz also reported the satisfactory synthesis of 3-propionylindole (**111**) and 3-acetyl-5-benzyloxyindole (**115**) by this procedure, the reactions being carried out in a benzene–ether mixture.[68]

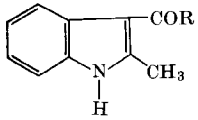
3-Acetyl-2-methylindole (**116**) can readily be obtained by the action of acetyl chloride on the 2-methylindole Grignard reagent in ether.[69–71]

[64] B. Oddo and L. Sessa, *Gazz. Chim. Ital.* **41**, 234 (1911); *Chem. Abstr.* **5**, 2638 (1911)
[65] S. Hishida, *Nippon Kagaku Zasshi* **72**, 312 (1951); *Chem. Abstr.* **46**, 5038 (1952).
[66] J. W. Baker, *J. Chem. Soc.* p. 461 (1946).
[67] J. E. Saxton, *J. Chem. Soc.* p. 3592 (1952).
[68] J. Szmuszkovicz, *J. Am. Chem. Soc.* **82**, 1180 (1960).
[69] B. Oddo, *Gazz. Chim. Ital.* **43**, 190 (1913); *Chem. Abstr.* **8**, 85 (1914).
[70] A. H. Salway, *J. Chem. Soc.* **103**, 351 (1913).
[71] R. V. Jardine and R. K. Brown, *Can. J. Chem.* **41**, 2067 (1963).

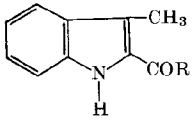
2-Acetyl-3-methylindole (**117**) was obtained when the skatole Grignard reagent was treated with acetyl chloride at 100° in the absence of solvent, but 1-acetyl-3-methylindole (**118**) was obtained when the



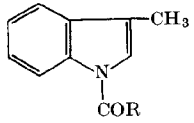
(**115**)



(**116**) R = CH_3
(**121**) R = C_2H_5
(**122**) R = n-C_3H_7



(**117**) R = CH_3
(**120**) R = C_2H_5

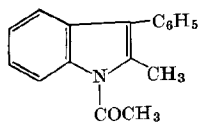


(**118**) R = CH_3
(**119**) R = C_2H_5

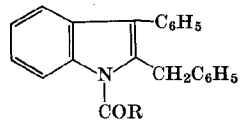
reaction was carried out for 12 days at 0°.[69] Both 3-methyl-1-propionylindole (**119**) and 3-methyl-2-propionylindole (**120**) were obtained analogously by the action of propionyl chloride on the skatole Grignard reagent. 2-Methyl-3-propionylindole (**121**) and 2-methyl-3-n-butyrylindole (**122**) were also prepared by the action of propionyl and n-butyryl chloride on the Grignard reagent from 2-methylindole.[69]

Bruce and Sutcliffe obtained 1-acetyl-2-methyl-3-phenylindole (**123**) by the action of acetyl chloride on 2-methyl-3-phenylindole magnesium iodide in ether.[72] These authors were able to obtain 1-benzoyl-2-benzyl-3-phenylindole (**124**) but not 1-acetyl-2-benzyl-3-phenylindole (**125**) from 2-benzyl-3-phenylindole magnesium iodide by analogous procedures.[72] 3-Acetyl-2-phenylindole (**126**)[16, 16a, 16b, 73] and 3-propionyl-2-phenylindole (**127**)[73] have recently been prepared in fair yield by the acylation of 2-phenylindole magnesium iodide with acetyl and propionyl chloride, respectively. Leete obtained a mixture of 1-acetyl-3-ethylindole (**128**) and 2-acetyl-3-ethylindole (**129**) by the interaction of acetyl chloride with 3-ethylindole magnesium iodide in ether.[74]

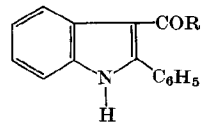
[72] J. M. Bruce and F. K. Sutcliffe, *J. Chem. Soc.* p. 4789 (1957).
[73] G. Buchmann and D. Rossner, *J. Prakt. Chem., Ser. 4*, **25**, 117 (1964).
[74] E. Leete, *J. Am. Chem. Soc.* **83**, 3645 (1961).



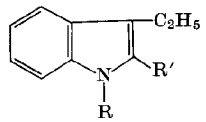
(**123**)



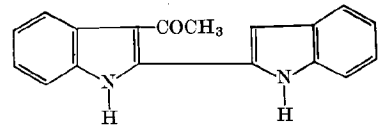
(**124**) R = C_6H_5
(**125**) R = CH_3



(**126**) R = CH_3
(**127**) R = C_2H_5



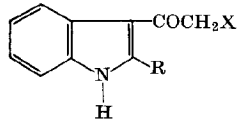
(**128**) R = $COCH_3$; R′ = H
(**129**) R = H; R′ = $COCH_3$



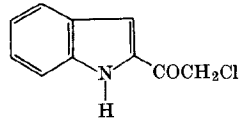
(**130**)

It has been reported that treatment of the Grignard reagent derived from 2,2′-biindole with acetyl chloride in ether in the cold gives a monoacetyl derivative, probably 3-acetyl-2,2′-biindole (**130**).[75]

b. *Halogen Substituted.* Salway reported in 1913 that 3-chloroacetyl-2-methylindole (**131**) could be obtained by the action of chloroacetyl chloride on 2-methylindole magnesium bromide; however, when the iodide was used in place of the bromide a mixture of approximately equal parts of **131** and 3-acetyl-2-methylindole (**116**) was obtained.[70] The dehalogenated product **116** was formed by the reducing action of the iodide ions, generated during the reaction, on the chloroacetyl



(**131**) R = CH_3; X = Cl
(**132**) R = H; X = Cl
(**133**) R = H; X = Br
(**134**) R = H; X = I
(**135**) R = CH_3; X = Br
(**136**) R = CH_3; X = I



(**137**)

derivative **131**. Majima and Kotake reported that 3-chloroacetylindole (**132**) was produced by the action of chloroacetyl chloride on indole magnesium iodide in 45% yield when the reaction was carried out at low temperatures in ether, but only in 4.8% yield in anisole.[11]

[75] W. Madelung and F. Hager, *Ber. Deut. Chem. Ges.* **49**, 2039 (1916).

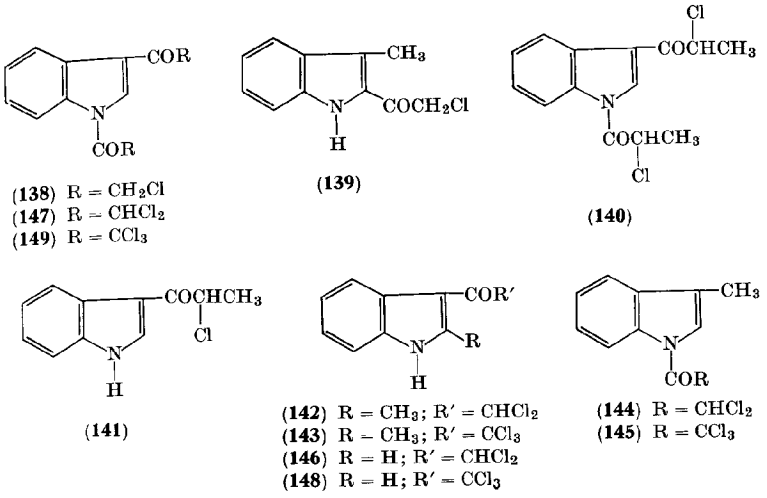
Sanna confirmed that **132** was readily obtained in ether in the cold.[76, 77] Sanna also prepared 3-bromoacetylindole (**133**) and 3-iodoacetylindole (**134**) by the action of bromoacetyl chloride and iodoacetyl chloride, respectively, on the indole Grignard reagent.[76, 77] The corresponding 3-halogenoacetyl-2-methylindole derivatives **131**, **135**, and **136** were obtained analogously from 2-methylindole.[76–78] In 1931 Mingoia claimed that, as well as 3-chloroacetylindole (**132**), a small quantity of an isomeric product, probably 2-chloroacetylindole (**137**), was obtained in the reaction with chloroacetyl chloride.[79] This compound was described as a 2-indolyl derivative since it gave indole-2-carboxylic acid on fusion with potassium hydroxide. It is possible that this conclusion was erroneous since indole-2-carboxylic acid has been obtained on alkaline fusion of other 3-indolyl derivatives (cf. Speeter and Anthony[80]). More recently, however, Ames *et al.* have stated that the main product of the reaction between indole magnesium bromide and chloroacetyl chloride in ether at 0° was 1,3-bis(chloroacetyl)indole (**138**) (m.p. 176°); small quantities of the monochloroacetyl derivative **132** (m.p. 230°) were formed at the same time.[81] They suggest that the melting point (214°) previously reported for **132**[11, 76, 77] was low because these products were essentially impure mixtures of **132** and **138** and that the product (m.p. 230°) obtained by Mingoia[79] and described as the 2-isomer (i.e., **137**) was, in fact, the 3-chloroacetyl derivative **132**.

Mingoia reported that 2-chloroacetyl-3-methylindole (**139**) was obtained by the action of chloroacetyl chloride on the skatole Grignard reagent.[79]

Kalir and Szara obtained 1,3-bis(α-chloropropionyl)indole (**140**) by the action of a 20% excess of α-chloropropionyl chloride on indole magnesium bromide in an ether–toluene mixture.[57] On the other hand, Ganellin and Ridley obtained 3-(α-chloropropionyl)indole (**141**) by the action of a 10% excess of α-chloropropionyl chloride on indole magnesium iodide in anisole.[16, 16a, 16b]

3-Dichloroacetyl-2-methylindole (**142**) and 3-trichloroacetyl-2-

[76] G. Sanna, *Gazz. Chim. Ital.* **59**, 838 (1929); *Chem. Abstr.* **24**, 2127 (1930).
[77] G. Sanna, *Gazz. Chim. Ital.* **59**, 169 (1929); *Chem. Abstr.* **23**, 4215 (1929).
[78] Q. Mingoia, *Gazz. Chim. Ital.* **59**, 105 (1929); *Chem. Abstr.* **23**, 3927 (1929).
[79] Q. Mingoia, *Gazz. Chim. Ital.* **61**, 646 (1931); *Chem. Abstr.* **26**, 1279 (1932).
[80] M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.* **76**, 6208 (1954).
[81] D. E. Ames, R. E. Bowman, D. D. Evans, and W. A. Jones, *J. Chem. Soc.* p. 1984 (1956).



(**138**) R = CH_2Cl
(**147**) R = $CHCl_2$
(**149**) R = CCl_3

(**139**)

(**140**)

(**141**)

(**142**) R = CH_3; R′ = $CHCl_2$
(**143**) R = CH_3; R′ = CCl_3
(**146**) R = H; R′ = $CHCl_2$
(**148**) R = H; R′ = CCl_3

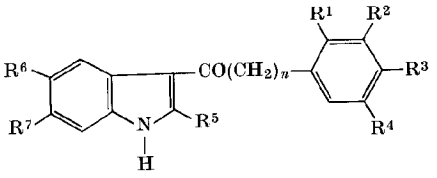
(**144**) R = $CHCl_2$
(**145**) R = CCl_3

methylindole (**143**) can be obtained in excellent yield by the action of dichloro- and trichloroacetyl chloride, respectively, on the 2-methylindole Grignard reagent.[82] Sanna and his colleagues later studied the action of dichloroacetyl chloride and trichloroacetyl chloride on the magnesium derivatives of indole and skatole.[83, 84] In the latter case no evidence of 2-substitution was forthcoming, the products being 1-dichloroacetyl-3-methylindole (**144**) and 1-trichloroacetyl-3-methylindole (**145**), respectively. The trichloro compound **145** decomposed in aqueous solution to give skatole, carbon dioxide, and chloroform.[84] In the case of indole, Sanna obtained 3-mono- and 1,3-disubstituted indoles by the action of di- and trichloroacetyl chloride on the Grignard reagent. In the former case 3-dichloroacetylindole (**146**) and 1,3-bis(dichloroacetyl)indole (**147**) were formed and in the latter case the analogous trichloroacetyl derivatives **148** and **149** were obtained.[83]

c. *Aryl Substituted.* A number of arylalkyl 3-indolyl ketones have been prepared by the coupling of a suitable arylalkyl acid chloride

[82] G. Sanna, *Gazz. Chim. Ital.* **61**, 60 (1931); *Chem. Abstr.* **25**, 2720 (1931).
[83] G. Sanna, *Rend. Seminario Fac. Sci. Univ. Cagliari* **4**, 28 (1934); *Chem. Abstr.* **30**, 6363 (1936).
[84] G. Sanna and F. Athene, *Rend. Seminario Fac. Sci. Univ. Cagliari* **4**, 62 (1934); *Chem. Abstr.* **30**, 6364 (1936).

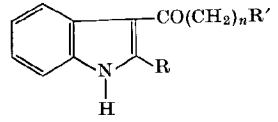
TABLE II



Compound number	R^1	R^2	R^3	R^4	R^5	R^6	R^7
150	H	OCH_3	OCH_3	H	H	H	H
151	NO_2	H	OCH_3	OCH_3	H	H	H
152	H	OCH_3	OCH_3	H	CH_3	H	H
153	NO_2	H	OCH_3	OCH_3	CH_3	H	H
154	H	OCH_3	OCH_3	H	H	Br	H
155	H	O—CH_2—O		H	H	H	H
156	H	O—CH_2—O		H	H	Br	H
157	NO_2	H	OCH_3	OCH_3	H	Br	H
158	NO_2	H	O—CH_2—O		H	H	H
159	NO_2	H	O—CH_2—O		H	Br	H
160	CH_3	OCH_3	OCH_3	H	H	H	H
161	OCH_3	OCH_3	H	H	H	H	H
162	H	OCH_3	H	H	H	H	H
163	Cl	OCH_3	OCH_3	H	H	H	H
164	H	OCH_3	OCH_3	Cl	H	H	H
165	Cl	H	OCH_3	OCH_3	H	H	H
166	Br	H	OCH_3	OCH_3	H	H	H
167	H	CH_3	CH_3	H	H	H	H
168	H	Cl	Cl	H	H	H	H
169	H	OCH_3	H	H	H	Br	H
170	H	OCH_3	OCH_3	Cl	H	Br	H
171	Br	H	OCH_3	OCH_3	H	Br	H
172	H	CH_3	CH_3	H	H	Br	H
173	H	O—CH_2—O		H	H	O—CH_2—O	
174	H	O—CH_2—O		H	CH_3	H	H
175	H	CH_3	CH_3	H	CH_3	H	H
176	H	Cl	Cl	H	CH_3	H	H
177	Cl	H	Cl	H	CH_3	H	H

with an indole Grignard reagent,[20–22, 85–87] usually derived from indole or 2-methylindole, although 5-bromoindole magnesium bromide has also been satisfactorily converted into 3-indolyl ketones by this procedure.[21] This reaction is usually carried out either in ether (at 34°)[22, 85–87] or in benzene–ether solutions, at temperatures below

TABLE III



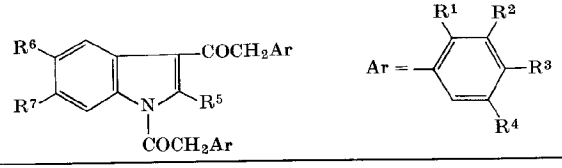
Compound number	R	R′	*n*
178	H	C_6H_5	2
179	CH_3	C_6H_5	2
180	H	4-ClC_6H_4	2
181	CH_3	4-$CH_3C_6H_4$	2
182	H	6-Tetralyl	2
183	CH_3	4-ClC_6H_4	2
184	CH_3	C_6H_5	3
185	H	4-$CH_3OC_6H_4$	0
186	H	2-ClC_6H_4	0
187	H	4-$C_2H_5C_6H_4$	0
188	CH_3	2-Furyl	0
189	H	1-Naphthyl	0
190	H	2-Naphthyl	0
191	H	1-Naphthyl	1
192	CH_3	2-Thienyl	0
193	CH_3	C_6H_5	1
194	CH_3	1-Naphthyl	1
195	H	4-$NO_2C_6H_4$	1

ambient.[20–22] Nearly 50 different 3-indolyl ketones (i.e., **150–195**) have been prepared in this manner (see Tables II and III). Young and Mizianti reported that the crude products obtained by the action of arylacetyl chlorides on the indole Grignard reagents were usually

[85] N. P. Buu-Hoï, N. Hoán, and N. D. Xuong, *J. Chem. Soc.* p. 3499 (1951).
[86] N. P. Buu-Hoï, E. Bisagni, R. Royer, and C. Routier, *J. Chem. Soc.* p. 625 (1957).
[87] S. Takagi, A. Sugii, and K. Machida, *Pharm. Bull. (Tokyo)* **5**, 617 (1957); *Chem. Abstr.* **52**, 16331 (1958).

either essentially the 1,3-bis(arylacetyl)indoles **196–200** (see Table IV) or mixtures of these products with the corresponding monoarylacetyl derivative shown in Table II. In the former case the 1,3-disubstituted indoles could readily be obtained in the pure state by recrystallization of the crude product. The five 1,3-bis(arylacetyl)indoles listed in Table IV were prepared in this manner. If this was not

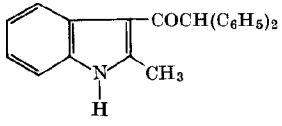
TABLE IV



Compound number	R^1	R^2	R^3	R^4	R^5	R^6	R^7
196	H	OCH_3	H	H	H	H	H
197	H	CH_3	CH_3	H	H	H	H
198	H	Cl	Cl	H	H	H	H
199	H	OCH_3	OCH_3	Cl	H	Br	H
200	H	CH_3	CH_3	H	H	Br	H

possible, the crude 1,3-bis(arylacetyl) derivatives were converted into the 3-monoarylacyl derivative by alkaline hydrolysis.[22]

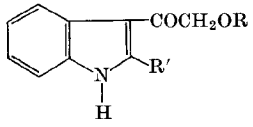
Benzhydryl 2-methyl-3-indolyl ketone (**201**) has been prepared by the action of diphenylacetyl chloride on 2-methylindole magnesium iodide.[88]



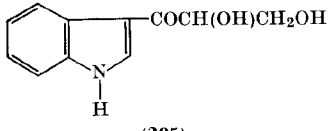
(**201**)

$C_2H_5OCH_2COCl$

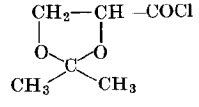
(**202**)



(**203**) R = C_2H_5; R′ = CH_3
(**204**) R = $C_6H_5CH_2$; R′ = H



(**205**)



(**206**)

[88] J. Szmuszkovicz, *J. Org. Chem.* **27**, 511 (1962).

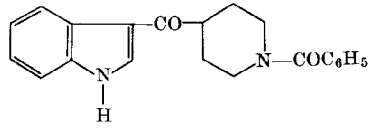
d. *Miscellaneous. i. Ethoxyacetyl chloride* (*o*-ethylglycolyl chloride). Ethoxyacetyl chloride (**202**) reacts readily with 2-methylindole magnesium bromide in ether to give a crystalline product, probably 3-ethoxyacetyl-2-methylindole (**203**).[89]

ii. Benzyloxyacetyl chloride. More recently Suvorov *et al.* have prepared 3-benzyloxyacetylindole (**204**) in an analogous manner by the action of benzyloxyacetyl chloride on indole magnesium iodide.[90]

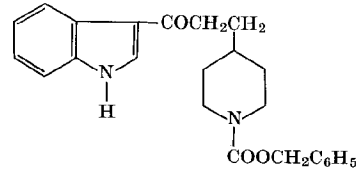
iii. Isopropylideneglyceroyl chloride. 3-(α,β-Dihydroxypropionyl)-indole (**205**) has recently been obtained by hydrolysis of its isopropylidene derivative which, in turn, was produced by the action of isopropylideneglyceroyl chloride (**206**) on indole magnesium iodide in ether.[91]

iv. N-Benzoylisonipecotoyl chloride. 3-(*N*-Benzoylisonipecotoyl)-indole (**207**) can be prepared by the action of *N*-benzoylisonipecotoyl chloride on indole magnesium bromide in ether.[63]

v. β-(1-*Carbobenzoxy*-4-*piperidyl*)*propionyl chloride.* β-(*N*-carbobenzyloxy-4-piperidyl)ethyl 3-indolyl ketone (**208**) was obtained similarly by the condensation of β-(*N*-carbobenzoxy-4-piperidyl)-propionyl chloride with indole magnesium bromide in ether.[92]



(**207**)



(**208**)

2. *Esters of Aliphatic Monocarboxylic Acids*

a. *Simple.* In 1915 Alessandri[93] reported that low yields of what were probably the 3-formyl derivatives of indole and 2-methylindole

[89] A. Sanna and G. Chessa, *Gazz. Chim. Ital.* **58**, 121 (1928); *Chem. Abstr.* **22**, 2562 (1928).

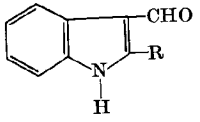
[90] N. N. Suvorov, K. B. Kholodkovskaya, and M. N. Preobrazhenskaya, *Khim. Geterotsikl. Soedin. Akad. Nauk Latv. SSR*, 1965 p. 265; *Chem. Abstr.* **63**, 6949 (1965).

[91] M. N. Preobrazhenskaya, K. B. Kholodkovskaya, and N. N. Suvorov, *Sin. Prir. Soedin. Ikh Analogov Fragmentov Akad. Nauk SSSR, Otd. Obshch. Tekh. Khim.*, 1965 p. 233; *Chem. Abstr.* **65**, 2200 (1966).

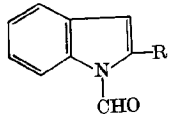
[92] J. I. DeGraw and J. G. Kennedy, *J. Heterocyclic Chem.* **3**, 90 (1966).

[93] L. Alessandri, *Atti Accad. Nazl. Lincei Mem. Classe Sci. Fis. Mat. Nat.* **24**[II], 194 (1915); *Chem. Abstr.* **10**, 1350 (1916).

(i.e., **209** and **210**) were obtained by the action of ethyl formate on the Grignard reagents derived from indole and 2-methylindole. In each case isomeric by-products, probably the corresponding *N*-formyl derivatives (**211** and **212**), were formed in significant yield. A few years later Alessandri and Passerini prepared 1-formyl-2-methylindole (**212**) and 3-formyl-2-methylindole (**210**) by the action of isoamyl formate on 2-methylindole magnesium iodide under mild conditions.[94]



(**209**) R = H
(**210**) R = CH_3



(**211**) R = H
(**212**) R = CH_3

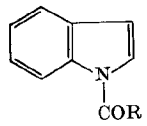
In 1922 Majima and Kotake reported that 3-formylindole (**209**) could be obtained in yields of up to 40% by the action of a fivefold excess of ethyl formate on indole magnesium iodide in anisole at low temperatures. However, they also claimed that only traces of the aldehyde were obtained when the reaction was carried out in ether.[10, 11]

In 1927 Putochin studied the effect of temperature on the nature of the products formed when the formylation reaction was carried out in benzene and observed that 1-formyl derivatives were the major products obtained at low temperatures, whereas the 3-formyl derivatives predominated at higher temperatures.[13] Britton *et al.* in 1947 claimed that the formation of the 3-formylindole derivative is probably favored, relative to the alternate 1-formylation process, by elevated temperatures and pressures.[95] However, it was apparently not possible to suppress completely the formation of the 1-formyl derivatives and yields of the order of 40% of both products were usually obtained.[95]

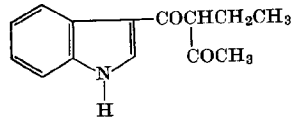
1-Acetylindole (**213**) was obtained by the action of ethyl acetate on indole magnesium iodide at low temperatures; slightly higher yields were obtained when the reaction was carried out in anisole rather than in ether.[96] Putochin subsequently observed that when the reaction was carried out in benzene at 85° both **213** and 3-acetylindole (**109**)

[94] L. Alessandri and M. Passerini, *Gazz. Chim. Ital.* **51**, 262 (1921); *Chem. Abstr.* **16**, 94 (1922).
[95] E. C. Britton, J. E. Livak, and J. C. Vander Weele, U.S. Patent No. 2,414,715 (1947); *Chem. Abstr.* **41**, 3129 (1947).
[96] R. Majima and T. Shigematsu, *Ber. Deut. Chem. Ges.* **57B**, 1449 (1924).

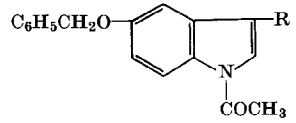
were formed.[13] Horiie reported that **213** was the only product formed when the reaction was carried out in refluxing ether[97]; with ethyl propionate in place of ethyl acetate, 1-propionylindole (**214**) was obtained.[98, 98a]



(**213**) R = CH_3
(**214**) R = C_2H_5



(**215**)



(**216**) R = H
(**217**) R = CH_3

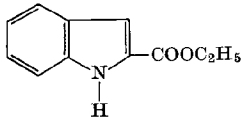
3-(α-Acetyl-*n*-butyryl)indole (**215**) was obtained by the action of ethyl α-ethylacetoacetate on indole magnesium bromide.[65]

Recently two further examples of the 1-acetylation of indoles by this route have been observed by Heacock and Hutzinger. 1-Acetyl-5-benzyloxyindole (**216**) and 1-acetyl-5-benzyloxy-3-methylindole (**217**) were obtained by the action of ethyl acetate on the relevant indole Grignard reagents at low temperatures.[98, 98a]

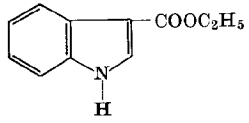
b. *Halogen Substituted.* The main product obtained from the reaction of indole magnesium iodide with ethyl chloroformate was originally described by Oddo and Sessa in 1911 as 2-ethoxycarbonylindole (**218**).[64] Some years later Majima and Kotake reported that this product was not **218** but the isomeric 3-ethoxycarbonylindole (**219**) which could be obtained in yields of up to 78% under ideal conditions.[11, 99] The Japanese authors further reported that some 1,3-di-(ethoxycarbonyl)indole (**220**) was also invariably formed along with **219** during the course of the reaction and that when the reaction was

[97] S. Horiie, *Mem. Inst. Sci. Ind. Res. Osaka Univ.* **7**, 143 (1950); *Chem. Abstr.* **45**, 9030 (1951).
[98] R. A. Heacock and O. Hutzinger, unpublished observations, 1965.
[98a] O. Hutzinger, Ph.D. Thesis, Univ. of Saskatchewan, Saskatoon, Saskatchewan, Canada, 1965.
[99] R. Majima and M. Kotake, *Ber. Deut. Chem. Ges.* **63B**, 2237 (1930).

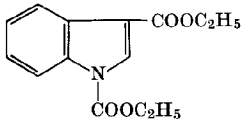
carried out with a 2:1 molecular ratio of ester to indole, significant quantities of the diester **220** were formed.[99] The preparation of **219** by what was essentially Majima and Kotake's procedure has subsequently been described by other workers.[100–102] Brown and Garrison[102] claimed that better results were obtained by carrying out the reaction between $-15°$ and $-5°$ than at the temperature reported by the Japanese workers (i.e., up to 35°) (cf. ref. 99). However, a recent study[103] of the reaction between ethyl chloroformate and indole magnesium iodide has shown that both **219** and 1-ethoxycarbonyl-



(218)



(219)



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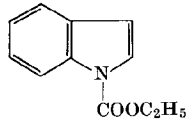
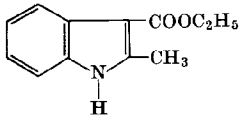
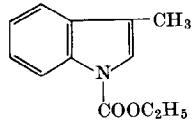


(221)



(222)



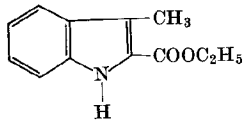
(223)

indole (**221**) are formed when the reaction is carried out with either 1 or 2 moles of ethyl chloroformate. The formation of **221** was favored at low temperatures (e.g., $-10°$), whereas the maximum yields of **219** were obtained at 10°. Significant quantities of the diester **220** were only formed when the reaction was carried out with two equivalents of the chloroformic ester at 35°.[103]

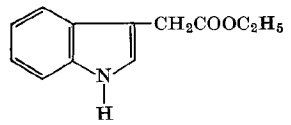
3-Ethoxycarbonyl-2-methylindole (**222**) and 1-ethoxycarbonyl-3-methylindole (**223**) were the main products said to be obtained by the action of ethyl chloroformate on the 2- and 3-methylindole Grignard

[100] E. Leete and L. Marion, *Can. J. Chem.* **31**, 775 (1953).
[101] W. E. Noland and R. D. Rieke, *J. Org. Chem.* **27**, 2250 (1962).
[102] R. K. Brown and R. A. Garrison, *J. Am. Chem. Soc.* **77**, 3839 (1955).
[103] S. Kašpárek and R. A. Heacock, *Can. J. Chem.* **44**, 2805 (1966).

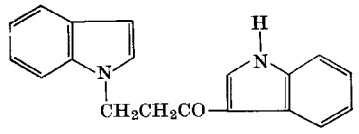
reagents in ether, respectively.[104] The ester **223** was still the main product formed when the latter reaction was carried out at 130°–140°. Under more vigorous conditions (i.e., 240°–250° for 3 hours, after removal of the solvent), a mixture of **223**, a small quantity of a second ester, probably 2-ethoxycarbonyl-3-methylindole (**224**), and their decomposition products were obtained.[104]



(224)



(225)



(226)

In an attempt to prepare ethyl 3-indolylacetate (**225**) by the action of ethyl chloroacetate on indole magnesium iodide, only unidentified oily products were obtained under a variety of different experimental conditions.[97] However, when indole magnesium iodide was treated with ethyl β-chloropropionate in ether, a product, identified as 3-[β-(1-indolyl)propionyl]indole (**226**) by its behavior on alkaline hydrolysis and by the number of active hydrogen atoms it contained, was obtained.[97]

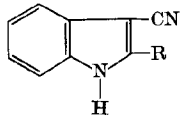
3. *Nitriles*

a. *Unsubstituted.* The indole Grignard reagents differ from most other Grignard reagents in their reactivity toward nitriles, in that they do not add to the cyano group in the usual manner.[105] Majima and Hoshino showed that indole magnesium iodide forms a stable addition product with acetonitrile which, although stable at 70°, is readily decomposed by water regenerating indole.[106]

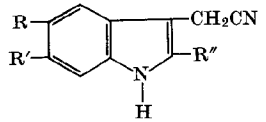
[104] B. Oddo, *Gazz. Chim. Ital.* **42**, 361 (1912); *Chem. Abstr.* **6**, 2234 (1912).
[105] The cyano group in 2-chloro-4-cyanopyridine does, however, appear to react in the expected manner with the indole Grignard reagent (see Section III, B, 7).
[106] R. Majima and T. Hoshino, *Ber. Deut. Chem. Ges.* **58B**, 2042 (1925).

b. *Halogenonitriles.* In 1924 Majima *et al.* found that cyanogen chloride reacts with the Grignard reagents derived from indole and 2-methylindole to give 3-cyanoindole (**227**) and 3-cyano-2-methylindole (**228**), respectively; these products were readily formed at low temperatures.[107] Only unidentified gummy products were obtained by the action of cyanogen bromide on the indole Grignard reagent.[108]

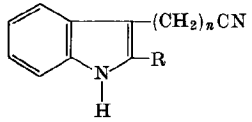
In 1925 Majima and Hoshino reported the formation of 3-indolylacetonitrile (**229**) by the action of chloroacetonitrile on indole magnesium iodide in anisole.[106] 2-Methyl-3-indolylacetonitrile (**230**) was obtained by the action of chloroacetonitrile on 2-methylindole magnesium iodide in ether.[37]



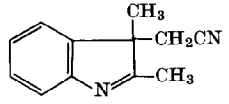
(**227**) R = H
(**228**) R = CH_3



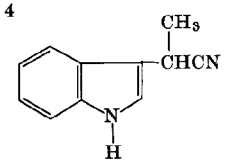
(**229**) R = R′ = R″ = H
(**230**) R = R′ = H; R″ = CH_3
(**231**) R = R″ = H; R′ = OCH_3
(**232**) R = OCH_3; R′ = R″ = H
(**233**) R = $OCH_2C_6H_5$; R′ = R″ = H



(**235**) R = H; $n = 2$
(**236**) R = H; $n = 3$
(**237**) R = CH_3; $n = 3$
(**238**) R = CH_3; $n = 4$



(**234**)



(**239**)

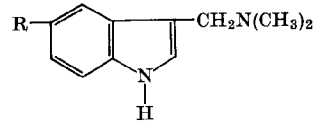
Akabori and Saito obtained 6-methoxy-3-indolylacetonitrile (**231**) from 6-methoxyindole and chloroacetonitrile by the Grignard reaction,[109] and Wieland *et al.* prepared 5-methoxy-3-indolylaceto-

[107] R. Majima, T. Shigematsu, and T. Rokkaku, *Ber. Deut. Chem. Ges.* **57B**, 1453 (1924).
[108] F. P. Doyle, W. Ferrier, D. O. Holland, M. D. Mehta, and J. H. C. Nayler, *J. Chem. Soc.* p. 2853 (1956).
[109] S. Akabori and K. Saito, *Ber. Deut. Chem. Ges.* **63B**, 2245 (1930).

nitrile (**232**) analogously.[110] The preparation of 5-benzyloxy-3-indolylacetonitrile (**233**) by the action of chloroacetonitrile on the 5-benzyloxyindole Grignard reagent in ether has also been described.[111,112] It has been claimed that this reaction is of wide applicability and that many substituted 5-benzyloxy-3-indolylacetonitriles can be prepared by this route.[111,112]

2,3-Dimethylindole magnesium iodide reacts with chloroacetonitrile in ether to give 3-cyanomethyl-2,3-dimethylindolenine (**234**).[37] Majima and Hoshino obtained 3-(2-cyanoethyl)indole (**235**) by the action of β-chloropropionitrile on indole magnesium iodide.[106] The reaction was slower with β-chloropropionitrile than with chloroacetonitrile.[106] 3-(3-Cyano-*n*-propyl)indole (**236**), required as an intermediate in the synthesis of 3-indolyl-γ-*n*-butyric acid, was prepared, but not isolated, by the action of γ-chloro-*n*-butyronitrile on indole magnesium iodide.[113]

Zenitz obtained the analogous compounds **237** and **238** by the action of the corresponding α-cyano-ω-bromo-*n*-alkanes on 2-methylindolyl magnesium bromide in ether.[48] Eiter and Svierak prepared α-(3-indolyl)propionitrile (**239**) by the action of α-bromopropionitrile on indole magnesium iodide in anisole.[58]



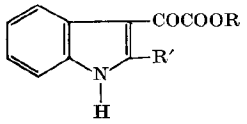
(**240**) R = H
(**241**) R = OCH_3

c. *Aminonitriles.* An interesting reaction of a nitrile with the indole Grignard reagent in which the cyano group reacts as a pseudohalogen was described by Wieland and Hsing.[114] Gramine (**240**) was readily obtained by the action of dimethylaminoacetonitrile on indole magnesium iodide in ether. The same authors prepared 3-dimethylaminomethyl-5-methoxyindole (**241**) in an analogous manner.[114]

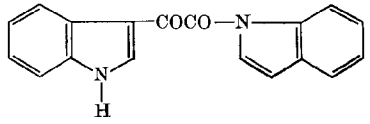
[110] H. Wieland, W. Konz, and H. Mittasch, *Ann. Chem.* **513**, 1 (1934).
[111] M. E. Speeter, U.S. Patent No. 2,703,325 (1955); *Chem. Abstr.* **50**, 1921 (1956).
[112] M. E. Speeter, U.S. Patent No. 2,728,778 (1955); *Chem. Abstr.* **50**, 10786 (1956).
[113] S. S. Nametkin, N. A. Dzbanovskii, and A. G. Rudney, *Compt. Rend. Acad. Sci. URSS* **32**, 333 (1941); *Chem. Abstr.* **37**, 3756 (1943).
[114] T. Wieland and C. Y. Hsing, *Ann. Chem.* **526**, 188 (1936).

4. *Aliphatic Dicarboxylic Acids*

a. *Ester Acid Chlorides.* Methoxalyl chloride reacts readily with indole magnesium iodide in the cold to give mainly methyl 3-indolylglyoxalate (**242**),[107, 115] accompanied by a small quantity of 1-(3-indolylglyoxalyl)indole (**243**).[107] Ethyl 3-indolylglyoxalate (**244**) and ethyl 2-methyl-3-indolylglyoxalate (**245**) were prepared in an ana-



(**242**) R = CH_3; R′ = H
(**244**) R = C_2H_5; R′ = H
(**245**) R = C_2H_5; R′ = CH_3

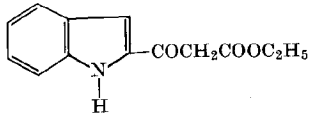


(**243**)

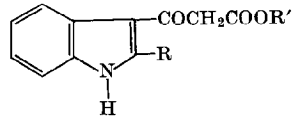
logous manner by the action of ethoxalyl chloride on the relevant indole Grignard reagent in ether.[116] In the case of the 2-methylindolyl derivative some doubt was expressed at that time about the structure of the product as it did not form a silver derivative.[116] The reaction between the indolyl magnesium halides and ethoxycarbonylacetyl chloride has been studied by several workers. Majima *et al.* reported that ethyl β-(3-indolyl)-β-oxopropionate (**246**) [which gave 3-acetylindole (**109**) on alkaline hydrolysis] was readily formed in the cold.[107] Oddo and Albanese confirmed the earlier reports of the Japanese workers that the ester **246** was the main product formed by this interaction, but under the more vigorous reaction conditions employed by the Italian workers a small quantity of a second product, possibly the isomeric 2-indolyl derivative (i.e., **247**) was also formed.[116] Albanese later described the synthesis of the analogous compound derived from 2-methylindole (i.e., **248**) by a similar procedure.[117]

[115] J. W. Baker, *J. Chem. Soc.* p. 458 (1940).
[116] B. Oddo and A. Albanese, *Gazz. Chim. Ital.* **57**, 827 (1927); *Chem. Abstr.* **22**, 1775 (1928).
[117] A. Albanese, *Gazz. Chim. Ital.* **60**, 21 (1930); *Chem. Abstr.* **24**, 4029 (1930).

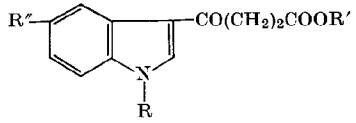
More recently Baker reported that indole magnesium bromide reacts readily in the cold with both methoxycarbonylacetyl chloride and ethoxycarbonylacetyl chloride. In the former case the main product was methyl β-(3-indolyl)-β-oxopropionate (**249**), accompanied by a small quantity of an unidentified substance $(C_{10}H_9ON)_x$; the ethyl ester **246** was the major product in the latter case.[66]



(**247**)



(**246**) R = H; R′ = C_2H_5
(**248**) R = CH_3; R′ = C_2H_5
(**249**) R = H; R′ = CH_3



(**250**) R = R″ = H; R′ = C_2H_5
(**251**) R = R″ = H; R′ = CH_3
(**252**) R = H; R′ = CH_3; R″ = OCH_3
(**253**) R = H; R′ = CH_3; R″ = Br
(**254**) R = R′ = R″ = H
(**255**) R = CH_3; R′ = R″ = H
(**256**) R = R′ = CH_3; R″ = H

Majima *et al.* prepared ethyl γ-(3-indolyl)-γ-oxobutyrate (**250**) in a similar manner by the condensation of the indole Grignard reagent with β-ethoxycarbonylpropionyl chloride.[107] Methyl γ-(3-indolyl)-γ-oxobutyrate (**251**) has been obtained by the action of β-methoxycarbonylpropionyl chloride on indole magnesium iodide in ether.[118, 119] Ballantine *et al.* prepared methyl γ-(5-methoxy-3-indolyl)-γ-oxobutyrate **252**[118] and Julia *et al.* obtained methyl γ-(5-bromo-3-indolyl)-γ-oxobutyrate (**253**)[120] by analogous procedures.

In 1966 Eraksina *et al.* obtained γ-(3-indolyl)-γ-oxobutyric acid (**254**) (cf. Section III,E,4,d) on alkaline hydrolysis of the ester **251**,

[118] J. A. Ballantine, C. B. Barrett, R. J. S. Beer, B. G. Boggiano, S. Eardley, B. E. Jennings, and A. Robertson, *J. Chem. Soc.* p. 2227 (1957).
[119] A. H. Jackson and P. Smith, *Chem. Commun.* p. 264 (1967).
[120] M. Julia, F. LeGoffic, J. Igolen, and M. Baillarge, *Compt. Rend.* **264**, 118 (1967).

prepared by the action of β-methoxycarbonylpropionyl chloride on indole in ether in the presence of anhydrous magnesium bromide at −10°.[121] This interesting reaction is probably mechanistically more similar to the Friedel–Crafts reaction than to a typical indole Grignard reaction. The 1-methyl derivative of the oxoacid **254** (i.e., **255**) was also obtained from the corresponding oxoester **256**, which was prepared analogously from 1-methylindole (**3**).[121]

b. *Diacid Chlorides.* In the early 1920's Oddo and Sanna reported that a number of different products were produced by the action of oxalyl chloride on indole magnesium bromide.[122, 123] The various compounds were formulated largely on the basis of the structures of their oxidation and hydrolysis products and on their ability or otherwise to form silver derivatives. Oddo and Sanna[122] initially reported the formation of bis(1,3-dicarbonylindol-1,3-diyl) (**257**), di(3-indolyl)-glyoxal (**258**), and di(1-indolyl)glyoxal (**259**).[124] The product **257** was reported to give **258** and **259** on alkaline hydrolysis. Indole-3-carboxylic acid was obtained on alkaline hydrolysis of the product described as di(3-indolyl)glyoxal (**258**); however, in the case of the isomeric glyoxal derivative **259**, indole-1-carboxylic acid was not isolated, but the hydrolysis products exhibited an odor of indole (**1**).[122] The following year Sanna claimed that, in addition to an unidentified compound (m.p., 163°) and the products described above, di(2-indolyl)glyoxal (**260**), bis(1,2-dicarbonylindol-1,2-diyl) (**261**), and 1-(3-indolylglyoxalyl)indole (**243**) were formed during the course of this reaction.[123]

Majima and Shigematsu later questioned the validity of some of the above structural assignments and claimed that the product described as di(1-indolyl)glyoxal (**259**) is actually 1-(3-indolylglyoxalyl)indole (**243**) since it gives **1** and 3-indolylglyoxalic acid (**262**) on alkaline hydrolysis.[96] The Japanese workers obtained di(1-indolyl)glyoxal (**259**) by the action of diethyl oxalate on the indole Grignard reagent

[121] V. N. Eraksina, A. N. Kost, T. S. Khazonava, and E. V. Vinogradova, *Khim. Geterotsikl. Soedin., Akad. Nauk Latv. SSR*, 1966 p. 226; *Chem. Abstr.* **65**, 2201 (1966).

[122] B. Oddo and G. Sanna, *Gazz. Chim. Ital.* **51**, 337 (1921); *Chem. Abstr.* **16**, 1423 (1922).

[123] G. Sanna, *Gazz. Chim. Ital.* **52**, 165 (1922); *Chem. Abstr.* **17**, 1639 (1923).

[124] These products were originally named "indil" derivatives, since they are structurally analogous to the better known compound "benzil" ($C_6H_5COCOC_6H_5$) and its derivatives.

(see Section III, C, 4, c) and they further claimed that the compound described as di(1-indolyl)glyoxal (**259**) by Oddo and Sanna[122] is, in fact, the isomeric di(2-indolyl)glyoxal (**260**).[96] In 1958 Millich and Becker[125] confirmed the finding of Majima and Shigematsu,[96] that the product described by Oddo and Sanna[122, 123] as di(2-indolyl)-glyoxal (**260**) was, in fact, di(3-indolyl)glyoxal (**258**). Millich and Becker reported that the compound described by the Italian authors was identical to a sample of **258** prepared by the action of 3-indolylglyoxalyl chloride on indole magnesium bromide at room temperature.[125]

The related compounds bis(2-methyl-3-indolyl)glyoxal (**263**)[122, 125] and bis(3-methyl-1-indolyl)glyoxal (**264**)[125] have been prepared by the action of oxalyl chloride on the Grignard reagents derived from 2-methylindole and 3-methylindole, respectively, Bis(1-methyl-3-indolyl)-glyoxal (**265**) was prepared by the action of oxalyl chloride on 1-methylindole in ether.[125]

Sanna reported that 1,3-di(3-indolyl)-1,3-dioxo-*n*-propane (**266**) and 1,4-di(3-indolyl)-1,4-dioxo-*n*-butane (**267**) were formed by the action of malonyl chloride and succinyl chloride, respectively, on the indole Grignard reagent in ether, and analogous products could be obtained from 2-methylindole.[126–128]

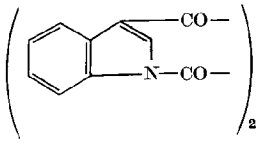
c. *Diesters.* Majima and Shigematsu observed that three products, namely di(1-indolyl)glyoxal (**259**), 1-(3-indolylglyoxalyl)indole (**243**), and ethyl 3-indolylglyoxalate (**244**), identified by their behavior on alkaline hydrolysis, were obtained by the action of diethyl oxalate on indole magnesium iodide in anisole. No identifiable products were isolated when the reaction was carried out with diethyl malonate instead of diethyl oxalate; however, a product described as 1,4-di(1-indolyl)-1,4-dioxo-*n*-butane (**268**) was isolated from the products obtained by the action of diethyl succinate on the indole Grignard reagent.[96] Several years later Hishida repeated this work using dimethyl oxalate instead of diethyl oxalate and ether as solvent in place of anisole.[65] With a reaction time of 30 minutes the main products were di(1-indolyl)glyoxal (**259**) and 1-(3-indolylglyoxalyl)-indole (**243**), in approximately equal amounts. However, when the

[125] F. Millich and E. I. Becker, *J. Org. Chem.* **23**, 1096 (1958).

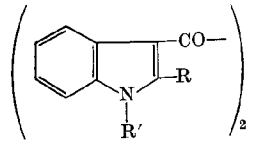
[126] G. Sanna, *Gazz. Chim. Ital.* **52**, 170 (1922); *Chem. Abstr.* **17**, 1639 (1923).

[127] G. Sanna, *Gazz. Chim. Ital.* **52**, 177 (1922); *Chem. Abstr.* **17**, 1639 (1923).

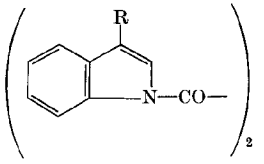
[128] G. Sanna, *Gazz. Chim. Ital.* **53**, 177 (1923); *Chem. Abstr.* **17**, 2883 (1923).



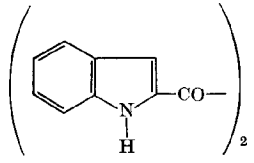
(257)



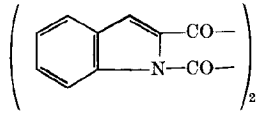
(258) R = R′ = H
(263) R = CH_3; R′ = H
(265) R = H; R′ = CH_3



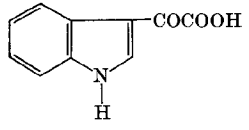
(259) R = H
(264) R = CH_3



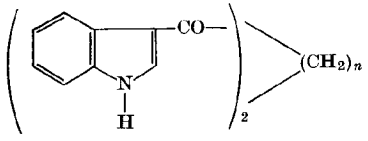
(260)



(261)



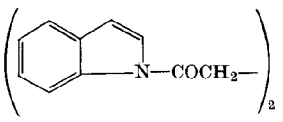
(262)



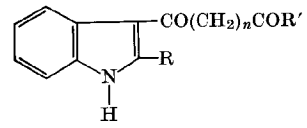
(266) $n = 1$ (267) $n = 2$
(269) $n = 4$ (270) $n = 8$

reaction was carried out for 11 hours, the major product formed was di(3-indolyl)glyoxal (**258**); small quantities of **243** being obtained as a by-product.[65]

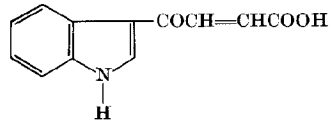
Hishida was unable to obtain any identifiable products when he attempted to extend this work to include the monoesters of several aliphatic dibasic acids. However, definite products (**269** and **270**) were obtained using diethyl adipate and diethyl sebacate, respectively. A second product containing only one indole residue (**271**) was also obtained in the latter case.[65]



(268)



(271) R = H; R′ = OC_2H_5; $n = 8$
(272) R = CH_3; R′ = OH; $n = 2$
(273) R = C_6H_5; R′ = OH; $n = 2$
(274) R = H; R′ = OH; $n = 3$
(278) R = H; R′ = $NHCH_3$; $n = 2$



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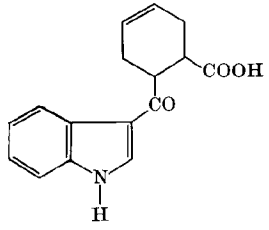

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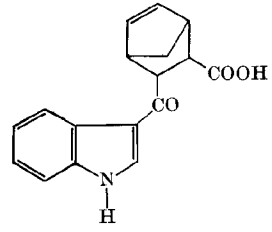


(277)

d. *Anhydrides.* γ-(3-Indolyl)-γ-oxobutyric acid (**254**) has been obtained by the action of succinic anhydride on indole magnesium halides in anisole.[129] The preparation of γ-(2-methyl-3-indolyl)-γ-oxobutyric acid (**272**) and the corresponding 2-phenylindolyl derivative **273** by analogous procedures has been described recently.

Kost *et al.* studied the interaction of indole magnesium iodide with a number of cyclic anhydrides of dibasic organic acids.[130] In addition to **254** the following 3-indolyloxo acids were prepared in this manner; δ-(3-indolyl)-δ-oxovaleric acid (**274**), γ-(3-indolyl)-γ-oxocrotonic acid

[129] A. P. Terent'ev, N. A. Dzbanovskii, and E. M. Urinovich, USSR Patent No. 119,189 (1959); *Chem. Abstr.* **54**, 2358 (1960).

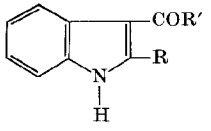
[130] A. N. Kost, V. N. Mitropol'skaya, S. L. Portnova, and V. A. Krasnova, *Zh. Obshch. Khim.* **34**, 2989 (1964); *Chem. Abstr.* **62**, 11761 (1965).

(**275**), *cis*-1-carboxy-2-(3-indolylcarbonyl)cyclohex-4-ene (**276**), and *cis*-2-carboxy-3-(3-indolylcarbonyl)norborn-5-ene (**277**).[130]

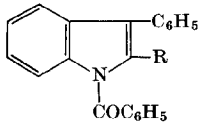
e. *Imides.* γ-(3-Indolyl)-*N*-methyl-γ-oxo-*n*-butyramide (**278**) was obtained when indole magnesium iodide was treated with *N*-methylsuccinimide in benzene.[131]

5. *Aromatic Monocarboxylic Acids*

a. *Acid Chlorides.* Oddo reported that 3-benzoylindole (**279**) was the main product obtained by the reaction of indole magnesium iodide



(**279**) R = H; R′ = C_6H_5
(**280**) R = CH_3; R′ = C_6H_5
(**281**) R = CH_3; R′ = 4-$CH_3C_6H_4$
(**282**) R = CH_3; R′ = 4-$C_2H_5C_6H_4$
(**283**) R = CH_3; R′ = α-naphthyl
(**284**) R = CH_3; R′ = β-naphthyl
(**285**) R = CH_3; R′ = 4-$CH_3OC_6H_4$



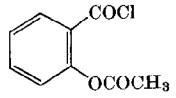
(**286**) R = CH_3
(**287**) R = $CH_2C_6H_5$

with benzoyl chloride.[2,69] More recently Buu-Hoï *et al.* have shown that a large number of simple 3-aroylindoles (i.e., **280–285**) can be readily obtained by the action of aroyl chlorides on indole magnesium bromide in ether.[86,132] Bruce and Sutcliffe obtained 1-benzoyl-2-methyl-3-phenylindole (**286**) and 1-benzoyl-2-benzyl-3-phenylindole (**287**) from the relevant indole Grignard reagents and benzoyl chloride.[72]

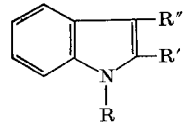
The action of *O*-acetylsalicyloyl chloride (**288**) on the simple indole

[131] Upjohn Co., Netherlands Patent Appl. 6,505,983, Nov. 12, 1965 [U.S. Patent Appl., May 11, 1964]; *Chem. Abstr.* **64**, 12646 (1966).
[132] N. P. Buu-Hoï, N. Hoán, and N. H. Khoi, *J. Org. Chem.* **15**, 131 (1950).

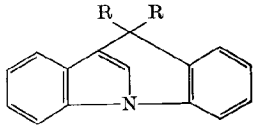
Grignard reagents was studied by Toffoli.[133,134] Two moles of 2-methylindole magnesium bromide and 1 mole of **288** gave mainly



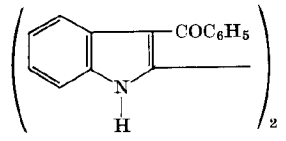
(**288**)



(**289**) R = H; R′ = CH_3; R″ = 2-HOC_6H_4CO
(**290**) R = R″ = H; R′ = 2-HOC_6H_4CO
(**291**) R = R″ = H; R′ = 2-HOC_6H_4CO
(**293**) R = 2-HOC_6H_4CO; R′ = H; R″ = CH_3
(**294**) R = H; R′ = 2-HOC_6H_4CO; R″ = CH_3



(**292**) R = 3-indolyl



(**295**)

2-methyl-3-salicyloylindole (**289**), together with lesser amounts of 3-acetyl-2-methylindole (**116**) and some unidentified by-products.[133,134] In the case where reaction occurred with 2 moles of the indole Grignard reagent the main products obtained were 3-salicyloylindole (**290**) and 3-acetylindole (**109**); smaller quantities of products described as 2-salicyloylindole (**291**) and a substance for which the unlikely structure **292** was proposed were also obtained.[134] Lower yields of the same products were obtained when equivalent quantities of the two reagents were allowed to react.[133,134] In the case of the skatole Grignard reagent the products obtained under analogous circumstances were 1-salicyloylskatole (**293**), 1-acetylskatole (**118**), and 2-salicyloylskatole (**294**).[134]

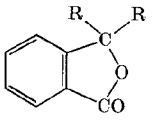
3,3′-Dibenzoyl-2,2′-biindole (**295**) was obtained by the action of benzoyl chloride on the 2,2′-biindole Grignard reagent.[75]

6. *Aromatic Dicarboxylic Acids*

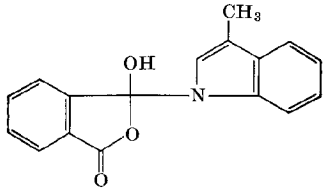
a. *Diacid Chlorides.* The only reactions reported so far between dibasic aromatic acid chlorides and indole Grignard reagents were des-

[133] C. Toffoli, *Gazz. Chim. Ital.* **64**, 364 (1934); *Chem. Abstr.* **28**, 6437 (1934).
[134] C. Toffoli, *Gazz. Chim. Ital.* **65**, 487 (1935); *Chem. Abstr.* **30**, 455 (1936).

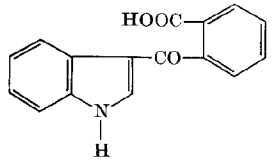
cribed by Oddo over 30 years ago.[135–137] 2-Methylindole magnesium bromide reacts with phthaloyl chloride to give "methylketolphthalein" (**296**) as the main product.[135, 136] An isomeric product, possibly derived from the isomeric (i.e., symmetrical) form of phthaloyl chloride, was formed at the same time.[135, 136] "Indolephthaleine" (**297**) was similarly obtained by the action of phthaloyl chloride on the indole Grignard reagent.[137] This product was possibly accompanied by some



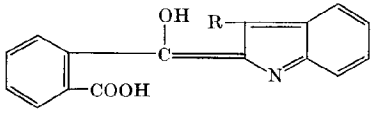
(**296**) R = 2-methyl-3-indolyl
(**297**) R = 3-indolyl
(**298**) R = 3-methyl-2-indolyl
(**299**) R = 3-methyl-1-indolyl



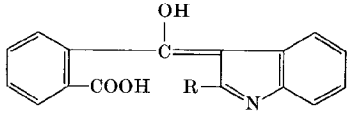
(**305**)



(**300**)



(**301**) R = H
(**304**) R = CH_3



(**302**) R = H
(**303**) R = CH_3

of the dehydrated uncyclized form[137] (cf. Sumpter and Miller[8]). The interaction of the skatole Grignard reagent (2 moles) with phthaloyl chloride gave both **298** and **299**.[138]

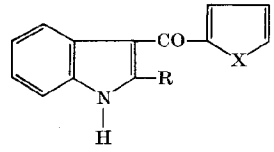
[135] B. Oddo, *Atti Accad. Nazl. Lincei Mem. Classe Sci. Fis. Mat, Nat.* **1**[VI], 236 (1925); *Chem. Abstr.* **19**, 2823 (1925).
[136] B. Oddo, *Gazz. Chim. Ital.* **56**, 437 (1926); *Chem. Abstr.* **21**, 241 (1927).
[137] B. Oddo, *Gazz. Chim. Ital.* **58**, 569 (1928); *Chem. Abstr.* **23**, 1634 (1929).
[138] B. Oddo and C. Toffoli, *Gazz. Chim. Ital.* **60**, 3 (1930); *Chem. Abstr.* **24**, 3784 (1930).

b. *Anhydrides.* Kost *et al.* recently reported that 2-(3-indolylcarbonyl)benzoic acid (**300**) (m.p. 196°) was obtained by the action of phthalic anhydride on indole magnesium iodide at 100°.[130] Many years previously Oddo and Toffoli had reported that two compounds, described as 2-carboxyphenyl-(2-indoleninylidene)methanol (**301**) (m.p. 155.5°) and the corresponding 3-indoleninylidene derivative (**302**) (179.5°), were obtained by the action of phthalic anhydride on the indole Grignard reagent.[138] In fact, **302** is merely a tautomeric form of **300**. The structures of these latter two compounds were not rigorously proved by the Italian workers and it is possible that the products **301** and **302** were, in fact, merely somewhat impure versions of **300**.

2-Carboxyphenyl-(2-methyl-3-indoleninylidene)methanol (**303**) was said to be formed by the action of phthalic anhydride on 2-methylindole magnesium bromide.[139] Skatole magnesium bromide, on the other hand, apparently gave 2-carboxyphenyl-(3-methyl-2-indoleninylidene)methanol (**304**) and 3-hydroxy-3-(3-methyl-1-indolyl)-phthalide (**305**) on treatment with 1 mole of phthalic anhydride. The derivative **305** was easily hydrolyzed in alkali, giving skatole and phthalic acid, and was thus formulated as a 1-skatolyl derivative.[138]

7. *Heterocyclic Acids*

a. *Acid Chlorides.* Buu-Hoï *et al.* prepared 3-(2-furoyl)-2-methylindole (**306**) and 2-methyl-3-(2-theonyl)indole (**307**) by the action of



(**306**) R = CH_3; X = O
(**307**) R = CH_3; X = S
(**308**) R = H; X = O

the acid chlorides derived from furan-2-carboxylic acid and thiophene-2-carboxylic acid, respectively, on 2-methylindole magnesium bromide in ether.[86]

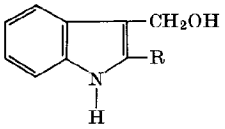
b. *Esters.* 3-(2-Furoyl)indole (**308**) was prepared by the action of 2-ethoxycarbonylfuran on indole magnesium bromide in ether.[65]

[139] B. Oddo and L. Perotti, *Gazz. Chim. Ital.* **56**, 442 (1926); *Chem. Abstr.* **21**, 242 (1927).

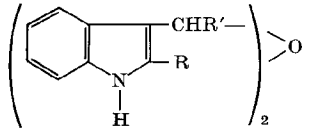
D. Reactions with Carbonyl Compounds

1. *Aldehydes*

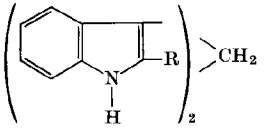
a. *Aliphatic.* Mingoia obtained two products by the action of formaldehyde on the indole Grignard reagent. One of the products had a melting point of 158° and was described as being 3-indolylmethanol (**309**); the second product, which did not melt, was considered to be



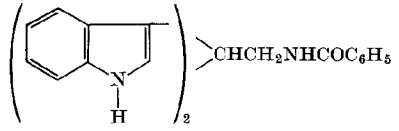
(**309**) R = H
(**312**) R = CH_3



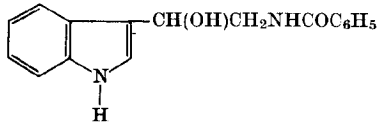
(**310**) R = R′ = H
(**313**) R = H; R′ = CH_3
(**314**) R = R′ = CH_3



(**311**) R = H
(**315**) R = CH_3



(**316**)



(**317**)

bis(3-indolylmethyl) ether (**310**).[140] This author also reported that the analogous 2-methylindolyl compounds were obtained by the action of formaldehyde on 2-methylindole magnesium bromide.[140] In 1953 Leete and Marion reported that repetition of Mingoia's procedure for the preparation of **309** merely gave a glassy solid with an indefinite high melting point.[100] The melting point of an authentic sample of **309**, prepared by an unambiguous route, was 99°–100°.[100] The product (m.p. 158°) obtained by Mingoia was probably di(3-indolyl)methane (**311**) (cf. Bader and Oroshnik,[141] Leete,[142] and

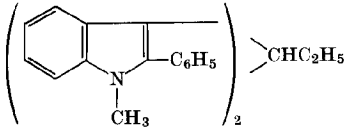
[140] Q. Mingoia, *Gazz. Chim. Ital.* **62**, 844 (1932); *Chem. Abstr.* **27**, 503 (1933).
[141] H. Bader and W. Oroshnik, *J. Am. Chem. Soc.* **81**, 163 (1959).
[142] E. Leete, *J. Am. Chem. Soc.* **81**, 6023 (1959).

Thesing[143]). The melting point (205°–206°) reported [140] for 2-methyl-3-indolylmethanol (**312**) is also higher than would have been expected.

Oddo and Cambieri reported that the interaction of equimolecular quantities of acetaldehyde and indole magnesium bromide and 2-methylindole magnesium bromide, respectively, under fairly vigorous reaction conditions, gave products which did not melt, but which decomposed above 300°, and which were described as bis[1-(3-indolyl)ethyl] ether (**313**) and bis[1-(2-methyl-3-indolyl)ethyl] ether (**314**), respectively.[144] Earlier Oddo and Toffoli had obtained di(3-indolyl)methane (**311**) and bis(2-methyl-3-indolyl)methane (**315**) by the action of 2 moles of the relevant indole Grignard reagents on 1 mole of acetaldehyde.[145] Apart from the different molecular ratios employed, the reaction conditions used (i.e., 1–2 hours under reflux in ether) were considerably milder than those subsequently used by Oddo and Cambieri (i.e., 10 hours at 100°–120°).[144]

In 1956 Ames *et al.* reported that a low yield of 1-benzamido-2,2-di-(3-indolyl)ethane (**316**) was obtained in an attempt to prepare 3-(2-benzamido-1-hydroxyethyl)indole (**317**) by the action of benzamidoacetaldehyde on indole magnesium iodide in ether.[81]

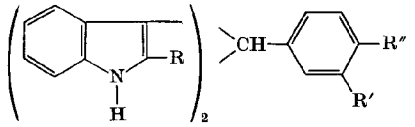
Buchmann and Trautmann reported recently that 1,1-bis(1-methyl-2-phenyl-3-indolyl)propane (**318**) was obtained by the action of propionaldehyde on the Grignard reagent derived from 1-methyl-2-phenylindole.[146] It is implied that a Grignard reagent is formed from the *N*-methylindole derivative in the usual manner. However, fairly vigorous reaction conditions were subsequently employed for interaction with the aldehyde (100°; 6 hours),[146] and the possibility that unchanged 1-methyl-2-phenylindole was the true reacting species, with the magnesium halide merely acting as a catalyst, cannot be excluded.



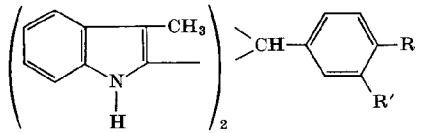
(**318**)

[143] J. Thesing, *Chem. Ber.* **87**, 692 (1954).
[144] B. Oddo and F. Cambieri, *Gazz. Chim. Ital.* **70**, 559 (1940); *Chem. Abstr.* **35**, 1050 (1941).
[145] B. Oddo and C. Toffoli, *Gazz. Chim. Ital.* **64**, 359 (1934); *Chem. Abstr.* **28**, 6436 (1934).
[146] G. Buchmann and P. Trautmann, *J. Prakt. Chem., Ser.* 4, **32**, 1 (1966).

b. *Aromatic.* Majima and Kotake obtained di(3-indolyl)phenylmethane (**319**) by the action of benzaldehyde on indole magnesium iodide[11]; later Mingoia reported the ready formation of a number of di(3-indolyl)phenylmethane derivatives by the interaction of several different aromatic aldehydes with the Grignard reagents derived from indole, 2-methylindole, and skatole.[147] The products (i.e., **320** and **321**) obtained from indole and from 2-methylindole (i.e., **322**, **323**, **324**, and **325**) were di(3-indolyl)phenylmethane derivatives, whereas the products derived initially from skatole were described as di(2-indolyl)phenylmethane derivatives (i.e., **326** and **327**).[147]



(**319**) R = R′ = R″ = H
(**320**) R = H; R′ = OH; R″ = OCH_3
(**321**) R = H; R′ + R″ = CH_2O_2
(**322**) R = CH_3; R′ = R″ = H
(**323**) R = CH_3; R′ = OH; R″ = OCH_3
(**324**) R = CH_3; R′ + R″ = CH_2O_2
(**325**) R = CH_3; R′ = H; R″ = NO_2



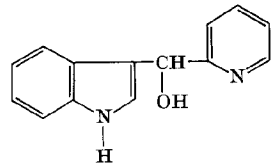
(**326**) R + R′ = CH_2O_2
(**327**) R = H; R′ = NO_2

Recent work by Powers has suggested that in addition to the di-indolylphenylmethane derivatives, 3-aroylindoles are obtained by the action of aromatic aldehydes on the indole Grignard reagents.[148]

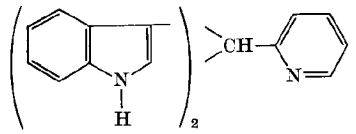
c. *Heterocyclic.* The reactions between indole magnesium bromide and several different heterocyclic aldehydes have been studied recently by Bader and Oroshnik.[141] Indole magnesium bromide reacts with 2-pyridinecarboxaldehyde at −25° in an ether–methylene dichloride mixture to give a 50% yield of 3-indolyl-2′-pyridylmethanol (**328**) together with a 5% yield of di(3-indolyl)-2-pyridylmethane (**329**).[141] However, when the reaction was carried out in the same solvent at 0°

[147] Q. Mingoia, *Gazz. Chim. Ital.* **56**, 772 (1926); *Chem. Abstr.* **21**, 1117 (1927).
[148] J. C. Powers, personal communication, 1967.

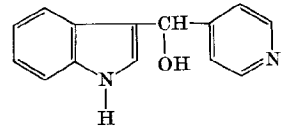
the yield of **328** dropped to 25%, whereas that of **329** increased to 44%.[141] The reaction with 4-pyridinecarboxaldehyde followed a somewhat similar course. At 0°, in the same solvent, 3-indolyl-4′-pyridylmethanol (**330**) was obtained in 58% yield.[141] However, at 25° with only ether as solvent the yield of **330** dropped to 22%, whilst at 60° the yield of **330** was further reduced to 6.5%.[141] In the higher



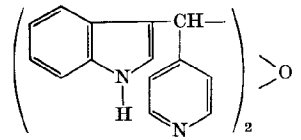
(**328**)



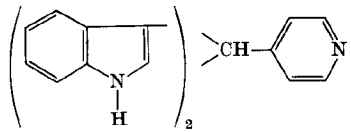
(**329**)



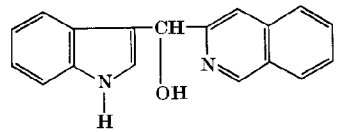
(**330**)



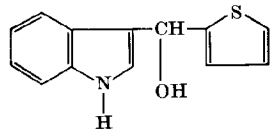
(**331**)



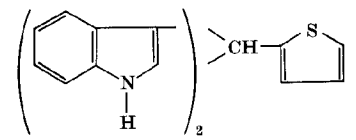
(**332**)



(**333**)



(**334**)



(**335**)

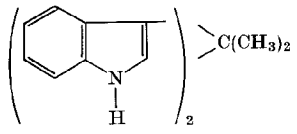
temperature reaction significant quantities of bis(3-indolyl-4′-pyridylmethyl)ether (**331**) (16%) and di(3-indolyl)-4′-pyridylmethane (**332**) (13%) were also obtained.[141]

3-Indolyl-3′-isoquinolylmethanol (**333**) (22%) and a small quantity of an unidentified by-product were formed by the action of 3-isoquinolinecarboxaldehyde on indole magnesium iodide in ether–methylene chloride at room temperature.[141] The expected methanol

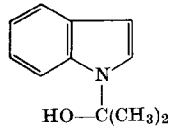
derivative **334** was not produced by the action of 2-thiophenecarboxaldehyde on indole magnesium iodide; however, a 28% yield of di(3-indolyl)-2-thienylmethane (**335**) was obtained.[141]

2. *Ketones*

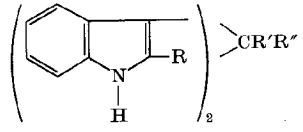
Majima and Kotake prepared 2,2-di(3-indolyl)propane (**336**) by the action of acetone on indole magnesium iodide in ether or anisole.[11] Recently 1-indolyl derivatives have been obtained as primary products by interaction of ketones with indole Grignard reagents[149]; for example acetone gave a 75% yield of 2-(1-indolyl)propan-2-ol (**337**).[149]



(**336**)



(**337**)



(**338**) R = R″ = CH_3
(**339**) R = R′ = CH_3; R″ = C_6H_5
(**340**) R = CH_3; R′ = R″ = C_3H_7
(**341**) R = R′ = CH_3; R″ = p-$CH_3C_6H_4$

Hoshino suggests that the isolation procedure used by Majima and Kotake[11] caused the decomposition of **337** into indole, acetone, and the diindolylpropane derivative **336**.[149]

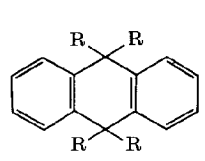
A number of diindolylmethane derivatives including **336**, **338**, **339**, **340**, and **341** have been obtained by the action of the appropriate ketones, under fairly vigorous conditions, on the Grignard reagents derived from indole or 2-methylindole.[150]

3. *Quinones and α-Diketones*

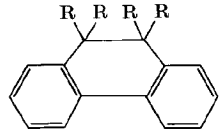
a. *Anthraquinone and Phenanthraquinone.* There are no reports in the literature concerning reactions of indole Grignard reagents with

[149] T. Hoshino, *Chem. Ber.* **85**, 858 (1952).
[150] B. Oddo and L. Perotti, *Gazz. Chim. Ital.* **60**, 13 (1930); *Chem. Abstr.* **24**, 3785 (1930).

simple quinones. However, the reactions of 2-methylindole magnesium bromide with two polycyclic quinones were studied about 40 years ago. 9,9,10,10-Tetrakis(2-methyl-3-indolyl)-9,10-dihydroanthracene

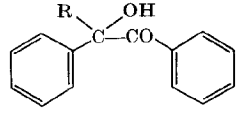


(**342**)

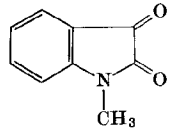


(**343**)

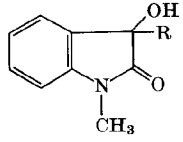
R = 3-indolyl



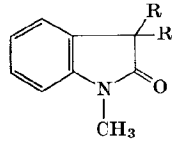
(**344**) R = 3-indolyl
(**345**) R = 3-methyl-2-indolyl



(**346**)



(**347**) R = 3-indolyl
(**349**) R = 2-methyl-3-indolyl
(**350**) R = 3-methyl-2-indolyl



(**348**) R = 3-indolyl

(**342**) and 9,9,10,10-tetrakis(2-methyl-3-indolyl)-9,10-dihydrophenanthrene (**343**) were obtained from anthraquinone and phenanthraquinone, respectively.[151, 152]

b. *Benzil and N-Methylisatin.* Benzil reacts with the indole Grignard reagent in ether at room temperature to give α-(3-indolyl)-benzoin (**344**). The skatole Grignard reagent reacted in an analogous manner to give **345**.[153] *N*-Methylisatin (**346**) reacts with indole magnesium iodide in benzene–ether to give a mixture of 1-methyl-3-(3-indolyl)dioxindole (**347**) and 1-methyl-3,3-di(3-indolyl)oxindole (**348**). The dioxindole derivatives **349** and **350** were obtained analogously.[153]

[151] Q. Mingoia, *Gazz. Chim. Ital.* **56**, 446 (1926); *Chem. Abstr.* **21**, 242 (1927).
[152] Q. Mingoia, *Gazz. Chim. Ital.* **58**, 673 (1928); *Chem. Abstr.* **23**, 3465 (1929).
[153] W. Steinkopf and H. Wilhelm, *Ann. Chem.* **546**, 211 (1941).

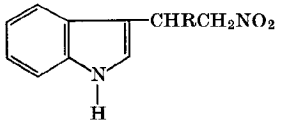
E. Reactions with Nitro Compounds

1. *Aromatic*

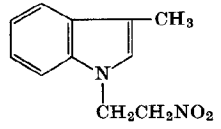
A crystalline addition product of indole with picryl chloride (i.e. 1-chloro-2,4,6-trinitrobenzene), together with an unidentified amorphous substance, were obtained by the action of picryl chloride on indole magnesium iodide, and analogous products were obtained in the reaction between the indole Grignard reagent and 1-chloro-2,4,5-trinitrobenzene.[154]

2. *Aliphatic*[155]

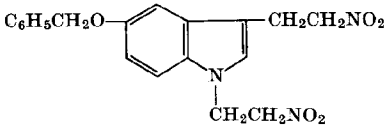
Indole magnesium iodide reacts with nitroethylene to give 3-(2-nitroethyl)indole (**351**) in good yield (Noland and Hartman[156]). Noland *et al.* subsequently showed that this reaction, which is usually carried out in ether at 0°, was of general applicability and reported



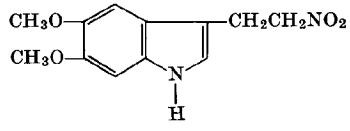
(**351**) R = H
(**352**) R = CH_3
(**353**) R = C_6H_5



(**354**)



(**355**)



(**356**)

that fairly good yields of 3-(1-methyl-2-nitroethyl)indole (**352**) and 3-(1-phenyl-2-nitroethyl)indole (**353**) were formed by the interaction of indole magnesium iodide and 1-nitroprop-1-ene and β-nitrostyrene, respectively.[157]

[154] M. Giua and G. Racciu, *Atti Accad. Sci. Torino, Classe Sci. Fis. Mat. Nat.* **67**, 121 (1932); *Chem. Abstr.* **26**, 5568 (1932).

[155] The reaction of ethyl nitrate with the indole Grignard reagent is discussed in Section III, F, 5, a (miscellaneous organic compounds).

[156] W. E. Noland and P. J. Hartman, *J. Am. Chem. Soc.* **76**, 3227 (1954).

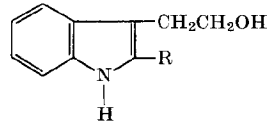
[157] W. E. Noland, G. M. Christensen, G. L. Sauer, and G. G. S. Dutton, *J. Am. Chem. Soc.* **77**, 456 (1955).

In 1961 Acheson and Hands obtained 3-methyl-1-(2-nitroethyl)-indole (**354**) in low yield by the addition of nitrocthylene to 3-methylindole magnesium iodide.[158] These authors also obtained 5-benzyloxy-1,3-bis(2-nitroethyl)indole (**355**) and 5,6-dimethoxy-3-(2-nitroethyl)-indole (**356**) by the action of nitroethylene on 5-benzyloxy- and 5,6-dimethoxyindole magnesium iodide, respectively. They excluded the possibility that the products **354**, **355**, and **356** had the isomeric indolenine structures on the basis of their absorption spectra and chemical properties.[158]

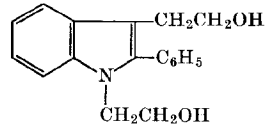
F. Reactions with Miscellaneous Organic Compounds

1. *Oxiranes*

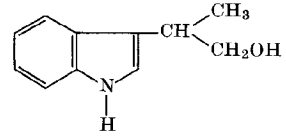
a. *Ethylene Oxide.* Tryptophol (**357**) has been obtained by the action of ethylene oxide on the indole Grignard reagent—first by Oddo and Cambieri[159] and later by Snyder and Pilgrim.[160] The former authors reported that it was necessary to heat the reaction mixture to 100°, after removal of the solvent, in order to obtain the desired



(**357**) R = H
(**358**) R = CH_3



(**359**)



(**360**)

product. 2-Methyltryptophol (**358**) was prepared from 2-methylindole magnesium bromide in a similar manner.[159] In 1966 Buchmann and Trautmann similarly obtained 1,3-bis(2-hydroxyethyl)-2-phenylindole (**359**) from 2-phenylindole.[146]

[158] R. M. Acheson and A. R. Hands, *J. Chem. Soc.* p. 744 (1961).

[159] B. Oddo and F. Cambieri, *Gazz. Chim. Ital.* **69**, 19 (1939); *Chem. Abstr.* **33**, 4239 (1939).

[160] H. R. Snyder and F. J. Pilgrim, *J. Am. Chem. Soc.* **70**, 1962 (1948).

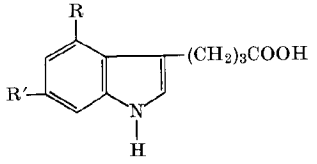
b. *Propylene Oxide.* Kalir and Szara have recently prepared 2-(3-indolyl)propan-1-ol (**360**) by the interaction of indole magnesium bromide with propylene oxide.[57]

2. *Aziridines*

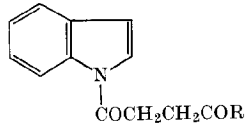
a. *Ethyleneimine.* Tryptamine (**23**) has recently been prepared by the action of ethyleneimine on indole magnesium bromide in boiling xylene.[161]

3. *Lactones*

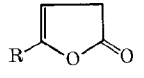
a. *Saturated.* γ-(3-Indolyl)-*n*-butyric acid (**361**) can be obtained by heating indole magnesium iodide with γ-butyrolactone.[162] Shagalov *et al.* have recently obtained γ-(4-chloro-3-indolyl)-*n*-butyric acid (**362**) and γ-(6-chloro-3-indolyl)-*n*-butyric acid (**363**) by analogous procedures.[163]



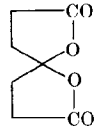
(**361**) R = R′ = H
(**362**) R = Cl; R′ = H
(**363**) R = H; R′ = Cl



(**364**) R = C_6H_5
(**366**) R = CH_3
(**368**) R = CH_2CH_2COOH



(**365**) R = C_6H_5
(**367**) R = CH_3



(**369**)

b. *Unsaturated.* In 1955 Katritzky and Robinson found 1-(β-benzoylpropionyl)indole (**364**) as the only identifiable product from

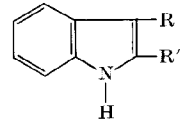
[161] R. Bucourt and M. Vignau, *Bull. Soc. Chim. France* p. 1190 (1961).
[162] F. N. Stepanov, USSR Patent No. 66,681 (1946); *Chem. Abstr.* **41**, 2087 (1947).
[163] L. B. Shagalov, N. P. Sorokina, and N. N. Suvorov, *Zh. Obshch. Khim.* **34**, 1592 (1964); *Chem. Abstr.* **61**, 5596 (1964).

the reaction between 4,5-dihydro-5-oxo-2-phenylfuran (**365**) and indole magnesium iodide.[164] The reaction was carried out under a wide variety of different experimental conditions and in all instances **364** was the major product obtained. 1-Laevuloylindole (**366**) was similarly obtained from α-angelicalactone (**367**). The products **364** and **366** were readily hydrolyzed by warm dilute alkali to indole and the corresponding acids; the absence of any N–H absorption bands in their infrared spectra confirmed that **364** and **366** were 1-indolyl derivatives.[164]

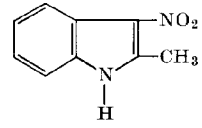
1-(6-Carboxy-4-oxohexanoyl)indole (**368**) was obtained analogously by the action of indole magnesium iodide on the dilactone (**369**) of γ-oxopimelic acid.[164]

4. *Peracids*

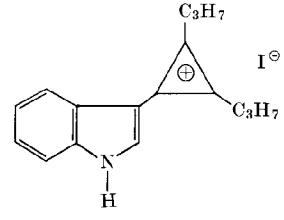
The oxidation of indole magnesium bromide and its 2- and 3-methyl derivatives at room temperature with *p*-nitroperbenzoic acid, in the absence of light and air, results in the formation of 3-bromoindole (**370**), 3-bromo-2-methylindole (**371**), and 2-bromo-3-methylindole (**372**), respectively.[165,166]



(**370**) R = Br; R′ = H
(**371**) R = Br; R′ = CH_3
(**372**) R = CH_3; R′ = Br



(**374**)



(**373**)

[164] A. R. Katritzky and R. Robinson, *J. Chem. Soc.* p. 2481 (1955).
[165] M. Mousseron-Canet and J.-P. Boca, *Compt. Rend.* **260**, 2263 (1965).
[166] M. Mousseron-Canet and J.-P. Boca, *Bull. Soc. Chim. France* p. 1294 (1967).

5. *Alkoxycyclopropenium Salts*

2-Aza-3,4-benzo-5,6-dipropylpentatriafulvalene hydriodide (**373**) was obtained in 20% yield by the action of 1,2-di-*n*-propyl-3-ethoxycyclopropenium fluoroborate on indole magnesium iodide in a methylene chloride–ether mixture.[167]

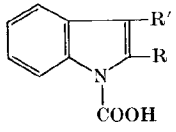
6. *Esters of Inorganic Acids*

a. *Ethyl Nitrate.* A compound described as 2-methyl-3-nitroindole (**374**) was said to be formed in low yield by the action of ethyl nitrate on 2-methylindole magnesium iodide.[4,93,94]

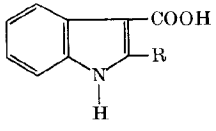
G. Reactions with Carbon Dioxide and Some Carbonic Acid Derivatives

1. *Carbon Dioxide*

Oddo and Sessa claimed that 1-carboxyindole (**375**) was obtained on treatment of indole magnesium iodide with gaseous carbon dioxide.[64] Majima and Kotake later reported that 3-carboxyindole (**376**) and not **375** was the main product obtained in this reaction[11]; improved yields of **376** were obtained when the reaction was carried out in anisole instead of ether.[11] Subsequently, several workers have employed essentially this procedure, for the synthesis of **376**.[108,168,169] It has recently been shown, however, that both the acids **375** and **376** are formed in approximately equal amounts by the carbonation of the indole Grignard reagent (Kašpárek and Heacock[170]).



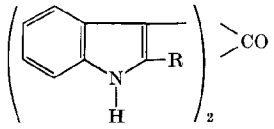
(**375**) R = R′ = H
(**377**) R = CH_3; R′ = H
(**379**) R = H; R′ = CH_3



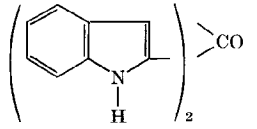
(**376**) R = H
(**378**) R = CH_3

[167] A. S. Kende, P. T. Izzo, and P. MacGregor, *J. Am. Chem. Soc.* **88**, 3359 (1966).
[168] M. S. Melzer, *J. Org. Chem.* **27**, 496 (1962).
[169] A. B. Durkee and J. C. Sirois, *J. Chromatog.* **13**, 173 (1964).
[170] S. Kašpárek and R. A. Heacock, *Can. J. Chem.* **45**, 771 (1967).

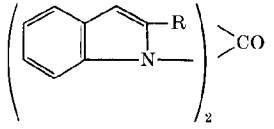
In 1912 Oddo reported the results of an investigation of the products obtained on carbonation of both the 2- and 3-methylindole Grignard reagents.[104] In the former case the relatively unstable 1-carboxy-2-methylindole (**377**) was the main product obtained when the reaction was carried out at temperatures up to 35°; however, at 110° the isomeric 3-carboxy-2-methylindole (**378**) was the major product formed. According to Oddo 1-carboxy-3-methylindole (**379**) is more stable than the corresponding 2-methyl compound (i.e., **377**) and can be obtained by carbonation of the skatole Grignard reagent at 100°.[104]



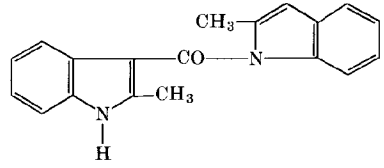
(**380**) R = H
(**383**) R = CH_3



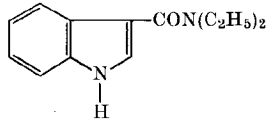
(**381**)



(**382**)



(**384**)



(**385**)

2. *Carbonyl Chloride*

The early literature on the reactions of the indole Grignard reagents with the simple diacid chlorides, in particular with carbonyl chloride and oxalyl chloride (see Section III,C,4,b), is both conflicting and confusing and much of the work reported warrants repetition since the evidence presented in support of many of the structural assignments made is not entirely convincing.

Oddo and Mingoia reported that di(3-indolyl) ketone (**380**), di(2-indolyl) ketone (**381**), and di(1-indolyl) ketone (**382**) were obtained by

the action of carbonyl chloride on indole magnesium bromide in ether.[171] These authors also reported that carbonyl chloride reacts with the 2-methylindole Grignard reagent to form bis(2-methyl-3-indolyl) ketone (**383**) and 2-methyl-1-indolyl 2′-methyl-3′-indolyl ketone (**384**).[171]

3. *Diethylcarbamoyl Chloride*

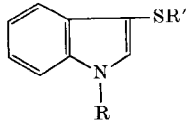
3-(*N*,*N*-Diethylcarbamoyl)indole (**385**) can be prepared by the action of diethylcarbamoyl chloride on indole magnesium iodide.[59]

For reactions with ethyl chloroformate see Section III, C, 2, b.

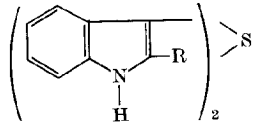
H. Reactions with Sulfur and Sulfur Compounds

1. *Elemental Sulfur and Inorganic Sulfur Compounds*

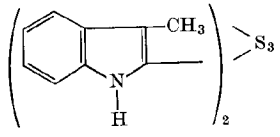
a. *Sulfur.* In an unsuccessful attempt to prepare thioindoxyl (**386**) by the interaction of indole magnesium bromide with sulfur at room temperature, Madelung and Tencer obtained a good yield of a diindolyl sulfide.[172] Although some of the chemical properties of this compound suggested it contained an —*N*—*S*—*N*— linkage, it was assumed that



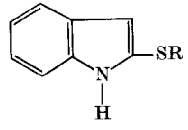
(**386**) R = R′ = H
(**390**) R = H; R′ = COC_6H_5
(**392**) R = R′ = $COCH_3$
(**393**) R = H; R′ = $COCH_3$
(**395**) R = $COCH_3$; R′ = 1-indolyl



(**387**) R = H
(**388**) R = CH_3



(**389**)



(**391**) R = COC_6H_5
(**394**) R = $COCH_3$

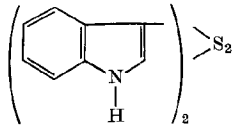
[171] B. Oddo and Q. Mingoia, *Gazz. Chim. Ital.* **57**, 473 (1927); *Chem. Abstr.* **22**, 77 (1928).
[172] W. Madelung and M. Tencer, *Ber. Deut. Chem. Ges.* **48**, 949 (1915).

the product was di(3-indolyl) sulfide (**387**) and not the isomeric di(1-indolyl) sulfide (cf. ref. 8, p. 53); this was later confirmed.[173] Bis(2-methyl-3-indolyl) sulfide (**388**) was obtained, in an analogous manner.[172] The interaction of sulfur with the skatole Grignard reagent follows a somewhat different course, giving, initially, bis(3-methyl-2-indolyl) trisulfide (**389**).[174]

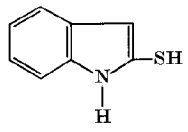
3-*S*-Benzoylthioindole (**390**) and 2-*S*-benzoylthioindole (**391**) were obtained together with **387** when indole magnesium bromide was treated successively with sulfur and benzoyl chloride.[175] A similar reaction occurred when acetyl chloride was used in place of benzoyl chloride. In this case 1-acetyl-3-(*S*-acetylthio)indole (**392**) was isolated after further acetylation of the crude products. 3-*S*-Acetylthioindole (**393**) could be obtained by saponification of **392**.[175] With minor modifications in the working-up procedure 2-*S*-acetylthioindole (**394**) and a compound described as 1-acetyl-3-indolyl 1′-indolyl sulfide (**395**) were said to be obtained. A compound described as thioindoxyl (**386**) was obtained on hydrolysis of the acylthio derivatives **390** and **393**.[175] The melting point (235°) reported by Oddo and Mingoia for **386** is much higher than would have been expected for a compound of this type. More recently Grant and Snyder have pointed out that this figure is quite close to that which they and other workers have obtained for di(3-indolyl) disulfide (**396**) prepared by alternate routes.[176–178] Oddo and Mingoia further claimed that thiooxindole (**397**) was obtained on alkaline hydrolysis of the 2-*S*-acylthioindole derivatives **391** and **394**.[175] In this case the melting point reported is close to that obtained for a sample of **397** prepared by the action of phosphorus pentasulfide on oxindole.[179]

By the consecutive action of sulfur and acetyl chloride on the 2-methylindole Grignard reagent Oddo obtained a violet solid (m.p 311°–312°), described as 3-*S*-acetylthio-2-methylindole (**398**), together

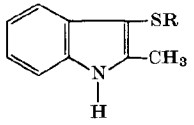
[173] R. V. Jardine and R. K. Brown, *Can. J. Chem.* **42**, 2626 (1964).
[174] B. Oddo and L. Raffa, *Gazz. Chim. Ital.* **71**, 242 (1941); *Chem. Abstr.* **36**, 2854 (1942).
[175] B. Oddo and Q. Mingoia, *Gazz. Chim. Ital.* **62**, 299 (1932); *Chem. Abstr.* **26**, 4603 (1932).
[176] M. S. Grant and H. R. Snyder, *J. Am. Chem. Soc.* **82**, 2742 (1960).
[177] W. Carpenter, M. S. Grant, and H. R. Snyder, *J. Am. Chem. Soc.* **82**, 2739 (1960).
[178] R. G. Woodbridge and G. Dougherty, *J. Am. Chem. Soc.* **72**, 4320 (1950).
[179] S. Sugasawa, I. Satoda, and J. Yamagisawa, *Yakugaku Zasshi* **58**, 139 (1938); *Chem. Abstr.* **32**, 4161 (1938).



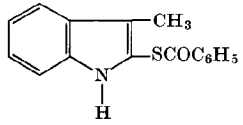
(396)



(397)

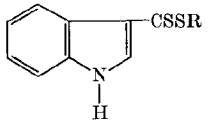


(398) R = $COCH_3$
(399) R = COC_6H_5

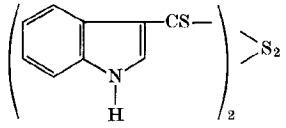


(400)

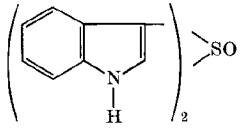
with some 3-acetyl-2-methylindole (**116**). [The product **116** was probably obtained by the interaction of some unchanged Grignard reagent with acetyl chloride (see Section III,C,1,a)]. The very high melting point and color reported[174] for **398** must throw some doubt on the structure assigned to this compound. Substances described as 3-*S*-benzoylthio-2-methylindole (**399**) and 2-*S*-benzoylthio-3-methylindole (**400**) were obtained in an analogous manner.[174] The reported



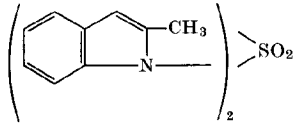
(401) R = H
(402) R = NH_4



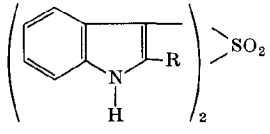
(403)



(404)



(405)



(406) R = H
(407) R = CH_3

melting points for **399** and **400** also seem not to be compatible with the structures originally assigned these compounds.

b. *Carbon Disulfide.* Oddo and Mingoia investigated the action of carbon disulfide on indole magnesium bromide and presumably obtained indole-3-dithiocarboxylic acid (**401**), which could be isolated only as the ammonium salt **402**. The tetrathio derivative **403** was invariably formed at the same time as the salt **402**. Analogous products were obtained from 2-methylindole magnesium bromide.[180]

c. *Sulfur Dioxide.* Di(3-indolyl) sulfoxide (**404**) was the main product obtained under a variety of experimental conditions by the action of sulfur dioxide on indole magnesium bromide.[4,172,180] In one instance the formation of di(3-indolyl) sulfide (**387**) as a by-product was also reported.[180] Bis(2-methylindolyl) sulfide (**388**) was the main product obtained analogously from 2-methylindole.[172,180] Oddo and Mingoia obtained a diindolyl sulfone (possibly **405**) by the action of sulfur dioxide on 2-methylindole magnesium bromide.[180]

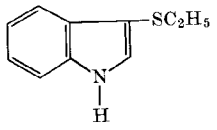
d. *Sulfur Dichloride.* Di(3-indolyl) sulfide (**387**) was obtained by the action of sulfur dichloride (SCl_2) on indole magnesium bromide. Di(3-indolyl) disulfide (**396**) could not be obtained in an analogous manner from disulfur dichloride.[172]

e. *Sulfuryl Chloride.* Di(3-indolyl) sulfone (**406**) and bis(2-methyl-3-indolyl) sulfone (**407**) were obtained by the controlled action of sulfuryl chloride on indole and 2-methylindole magnesium bromides, respectively.[180]

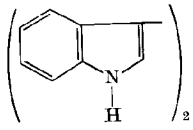
2. *Organic Sulfur Compounds*

a. *Ethanesulfenyl Chloride.* In 1965 Jardine and Brown reported that a mixture of products including ethyl mercaptan, di(3-indolyl) sulfide (**387**), 3-ethylindole (**5**), diethyl sulfide, 3-ethylthioindole (**408**), 3,3′-biindole (**409**), and di(3-indolyl) disulfide (**396**) was formed by the reaction of indole magnesium bromide with ethanesulfenyl chloride.[181] The mechanisms by which all these products are formed are not clear. 3-Ethylthioindole (**408**) was probably formed by a typical reaction between the Grignard reagent and the halogen compound. Indole (**1**) and diethyl sulfide were most likely obtained by hydrolysis

[180] B. Oddo and Q. Mingoia, *Gazz. Chim. Ital.* **56**, 782 (1926); *Chem. Abstr.* **21**, 1458 (1927).
[181] R. V. Jardine and R. K. Brown, *Can. J. Chem.* **43**, 1298 (1965).



(408)

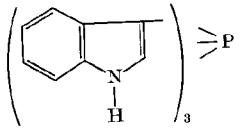


(409)

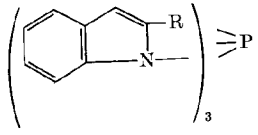
of unreacted starting materials. The 3,3′-biindole (**409**) could have been formed by oxidation of some unreacted Grignard reagent (see Section III,I,4).[181]

I. Reactions with Miscellaneous Inorganic Compounds

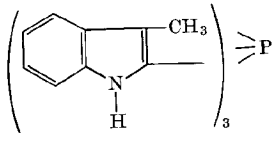
1. *Phosphorus Halides*



(410)



(411) R = H
(412) R = CH_3



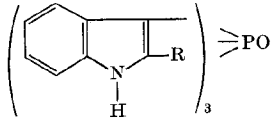
(413)

a. *Phosphorus Trichloride.* Tri(3-indolyl)phosphine (**410**) and tri(1-indolyl)phosphine (**411**) were obtained from indole magnesium bromide by the action of phosphorus trichloride.[182] Tris(2-methyl-1-indolyl)phosphine (**412**) and tris(3-methyl-2-indolyl)phosphine (**413**) were obtained analogously by the action of phosphorus trichloride on

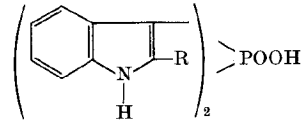
[182] Q. Mingoia, *Gazz. Chim. Ital.* **60**, 144 (1930); *Chem. Abstr.* **24**, 3783 (1930).

2- and 3-methylindole magnesium bromide, respectively. The formation of only one product in each instance was reported in these latter two cases.[182]

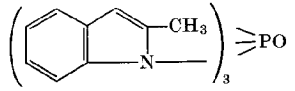
b. *Phosphorus Oxychloride.* Two products tri(3-indolyl)phosphine oxide (**414**) and di(3-indolyl)phosphinic acid (**415**) were formed by treatment of indole magnesium bromide with phosphorus oxychloride.[183] Tris(2-methyl-3-indolyl)phosphine oxide (**416**), tris(2-methyl-1-indolyl)phosphine oxide (**417**), and bis(2-methyl-3-indolyl)-phosphinic acid (**418**) were obtained in a similar reaction from 2-methylindole.[183]



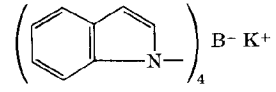
(414) R = H
(416) R = CH_3



(415) R = H
(418) R = CH_3



(417)



(419)

2. *Potassium Fluoroborate*

Potassium tetra(1-indolyl)boron (**419**) was obtained as an infusible white solid by boiling an ethereal solution of indole magnesium bromide with potassium fluoroborate under reflux for 6 hours.[184]

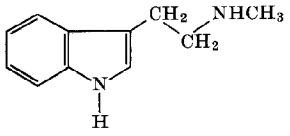
3. *Ferric Chloride*

An early report by Oddo suggested that a product containing two heterocyclic residues and one iron atom per molecule was obtained by the action of ferric chloride on the 2-methylindole Grignard reagent.[185]

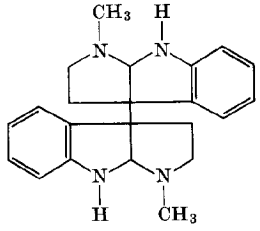
The formation of diphenyl on oxidation of phenyl magnesium bromide by anhydrous ferric chloride has been known for some

[183] Q. Mingoia, *Gazz. Chim. Ital.* **62**, 333 (1932); *Chem. Abstr.* **26**, 4813 (1932).
[184] V. A. Sazonova and V. I. Karpov, *Zh. Obshch. Khim.* **33**, 3313 (1963); *Chem. Abstr.* **60**, 4089 (1964).
[185] B. Oddo, *Gazz. Chim. Ital.* **44**, 268 (1914); *Chem. Abstr.* **9**, 795 (1915).

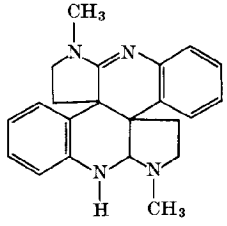
time [186] and this reaction has recently been utilized for biogenetic-type syntheses of some of the calycanthaceous alkaloids.[187] Hall *et al.* showed that treatment of N^{ω}-methyltryptamine (**420**) magnesium iodide with ferric chloride in anhydrous ether resulted in the formation of a number of dimeric products including *rac*- and *meso*-chimonanthine (**421**), *meso*-dehydro-β-calycanthine (**422**), and the isomeric



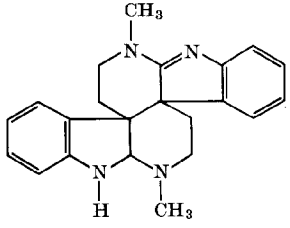
(**420**)



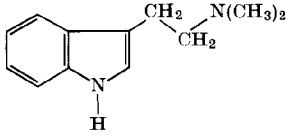
(**421**)



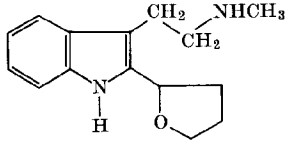
(**422**)



(**423**)



(**424**)



(**425**)

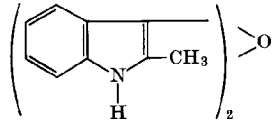
amidine **423**.[187] However, when the reaction was carried out in tetrahydrofuran in place of ether as solvent the yields of dimeric products were markedly reduced; the main products, in this case, were N^{ω},N^{ω}-dimethyltryptamine (**424**) (from excess of CH_3I in the Grignard reagent) and N^{ω}-methyl-2-(α′-tetrahydrofuranyl)tryptamine (**425**).[187]

[186] G. Champetier, *Bull. Soc. Chim. France* **47**, 1131 (1930).
[187] E. S. Hall, F. McCapra, and A. I. Scott, *Tetrahedron* **23**, 4131 (1967).

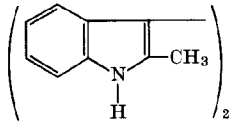
4. *Oxygen*

Toffoli obtained two products when 2-methylindole magnesium bromide was oxidized with oxygen in boiling ether solution, for 45 hours.[188,189] One was a yellow crystalline substance ($C_{18}H_{16}ON_2$, m.p. 208°), probably the same compound as that previously obtained by Oddo by the autoxidation of 2-methylindole and described as bis(2-methyl-3-indolyl) ether (**426**).[190] The second compound was probably 2,2′-dimethyl-3,3′-biindole (**427**); this latter compound was also obtained by the action of 2-methylindolyl magnesium bromide on the magnesium derivative of ethyl acetoacetate.[188] Toffoli also reported that a small quantity of an unidentified product (m.p., 255°–260°) was obtained on oxygenation of an ethereal solution of indole magnesium bromide for 25 hours.[188] More recently Jardine and Brown obtained chromatographic evidence for the formation of 3,3′-biindole (**409**) and at least nine other unidentified products, when a solution of the indole Grignard reagent was stirred in air at room temperature for 26 hours.[181]

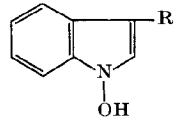
5. *Hydrogen Peroxide*



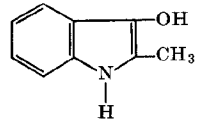
(**426**)



(**427**)



(**428**) R = H
(**429**) R = CH_3



(**430**)

Ingraffia studied the oxidation of the Grignard reagents derived from indole, skatole, and 2-methylindole with hydrogen peroxide and

[188] C. Toffoli, *Rend. Ist. Sanita Publica* **2**, 565 (1939); *Chem. Abstr.* **34**, 4733 (1940).
[189] C. Toffoli, *Atti 10th Congr. Intern. Chim., Rome, 1938* **3**, 369 (1939); *Chem. Abstr.* **33**, 9321 (1939).
[190] B. Oddo, *Gazz. Chim. Ital.* **50**, 268 (1920); *Chem. Abstr.* **15**, 2272 (1921).

reported that in all cases this resulted in the hydroxylation of the indole ring system. *N*-Hydroxylation was reported to occur with indole and skatole; 1-hydroxyindole (**428**) and 1-hydroxyskatole (**429**), respectively, being formed. 3-Hydroxy-2-methylindole (**430**) was formed in an analogous manner from the 2-methylindole Grignard reagent.[191] It should be noted, however, that Mousseron-Canet and Boca were unable to obtain *N*-hydroxyindoles by the oxidation of indole Grignard reagents with peracids.[166]

6. *Deuterium Oxide*

Jardine and Brown reported that the product obtained on treatment of indole magnesium iodide in ether with deuterium oxide in tetrahydrofuran was deuterated to the extent of about 50% in both the 1- and 3-positions of the indole nucleus.[71]

The reaction of the indole Grignard reagent with deuterium oxide has recently been studied in greater detail by Powers and his coworkers.[17,192] These workers observed that, similarly to the alkali metal salts of indole, the indole Grignard reagent undergoes essentially *N*-deuteration in tetrahydrofuran, but the Grignard reagent behaves differently from the other metal derivatives and undergoes 3-deuteration in ether solution. The amount of exchange that occurred in the 3-position was markedly affected by the amount of heavy water used. The optimum conditions for exchange at the 3-position involved the use of a moderate excess of deuterium oxide (ca. 5–7 equivalents). Smaller amounts or a large excess of D_2O gave only low yields of the 3-deuterated product; *N*-deuteration occurred under these conditions. Powers *et al.* explain their results by assuming that a complex between the Grignard reagent and D_2O is formed initially. In the presence of small amounts of D_2O, this complex is believed to be quite stable and exchanges very slowly. Since the conditions of work-up of these reaction mixtures all involved the use of a large excess of water, no *N*-deutero products would be detected and little 3-deuteration would be observed in this case. In the case where a large excess of D_2O was employed, the D_2O would increase the polarity of the medium and increase the dissociation of the N—MgX bond, which would lead to exchange occurring at the nitrogen atom. Where intermediate amounts

[191] F. Ingraffia, *Gazz. Chim. Ital.* **63**, 175 (1933); *Chem. Abstr.* **27**, 3710 (1933).
[192] J. C. Powers and W. P. Meyer, *Abstr. 149th Meeting Am. Chem. Soc., 1965* p. 56P, Abstr. No. 114.

of D_2O were used, a stable complex was assumed to be formed which gave rise to 3-deuteration, because solvation about the nitrogen atom may have prevented reaction at the nitrogen atom. Exchange at the 3-position was then presumed to occur through some form of intermediate indolenine complex.[17,192]

IV. Molecular Structure

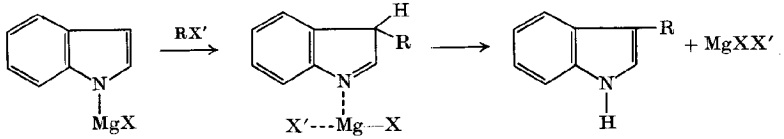
In the half-century that elapsed between its discovery in 1910[1] and the early years of the present decade, the structure of the indole Grignard reagent was the subject of sporadic speculation by a few authors. The conclusions reached by these early workers with regard to the structure of the indole magnesium halides were essentially based on the substitution behavior of these compounds. However, as a result of a number of recent systematic chemical and physicochemical investigations, much more is now known about their structure. Nevertheless, a considerable amount of further work will be required to resolve fully the twin problems of the structure and reactivity of the indole Grignard reagent. This is perhaps not too surprising since, as Ashby has pointed out in a recent review, the composition of Grignard reagents, in general, is one of the most fascinating and fundamental problems facing organic chemists today.[193]

Although Oddo was the initial discoverer of the indole Grignard reagents and despite the fact that Oddo and his collaborators carried out an extensive research program on the chemistry of these compounds between 1911 and 1941, these workers did not propose any particular structure for the indole Grignard reagent. Chelintzev and Tronov were the first workers to comment on the position of the magnesium residue in indole magnesium iodide, prepared from indole and propyl magnesium iodide. These workers suggested that the indole Grignard reagent could be regarded as either a C—MgX or an N—MgX species, but they did not attempt to distinguish between the two possibilities.[194] In 1930 Nenitzescu reported that indole magnesium iodide gave a negative color test with Michler's ketone and considered this fact as evidence that the indole Grignard reagent contained the

[193] E. C. Ashby, *Quart. Rev. (London)* **21**, 259 (1967).
[194] V. V. Chelintzev and B. V. Tronov. *Zh. Russ. Fiz. Khim. Obshchestva* **46**, 1876 (1914); *Chem. Abstr.* **9**, 2071 (1915).

N—MgX grouping.[195] This conclusion was based on the fact that pyrrole magnesium halides, which were regarded at that time as being C—MgX derivatives, gave violet colors with Michler's ketone. This test had been previously developed by Gilman and Schulze for detecting the presence of Grignard reagents containing the C—MgX grouping.[196] Other workers subsequently claimed that Nenitzescu's conclusions could be questioned on several grounds. Kharasch and Reinmuth suggested that pyrrole magnesium halides, regardless of their constitution, are capable of reacting with the carbonyl group of Michler's ketone (cf. ref. 9, p. 76); Gilman and Heck had pointed out earlier that color tests alone could not effectively differentiate between C—MgX and N—MgX structures in the case of the pyrrole Grignard reagent.[197]

In the 1930's a number of workers, including Hoshino,[30] Oddo,[198] and Kubota[50] suggested that indolenine-type intermediates (cf. **431**) were formed during the reaction of the indole Grignard reagents [depicted as N—MgX derivatives (cf. **432**)] with alkyl and arylalkyl halides. Rather surprisingly these were the last reports dealing with



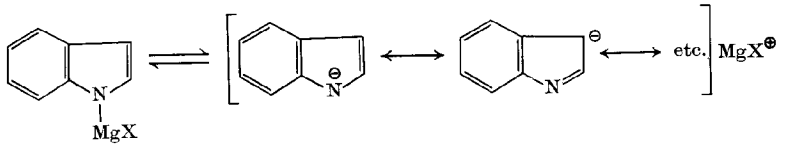
(432) **(431)**

the structure and reactivity of the indole Grignard reagents to appear for 30 years. During this period these reagents were alternatively depicted in the literature as C—MgX or N—MgX species (cf. refs. 8 and 199).

In the early 1960's Katritzky and Lagowski[200] and Badger[201] suggested that the indole Grignard reagents were essentially ionic

[195] C. D. Nenitzescu, *Bul. Soc. Chim. România* **11**, 130 (1930); *Chem. Abstr.* **24**, 2458 (1930).
[196] H. Gilman and F. Schulze, *J. Am. Chem. Soc.* **47**, 2002 (1925).
[197] H. Gilman and L. L. Heck, *J. Am. Chem. Soc.* **52**, 4949 (1930).
[198] B. Oddo, *Gazz. Chim. Ital.* **63**, 234 (1933); *Chem. Abstr.* **27**, 3933 (1933).
[199] P. L. Julian, E. W. Meyer, and H. C. Printy, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 3. Wiley, New York, 1952.
[200] A. R. Katritzky and J. M. Lagowski, "Heterocyclic Chemistry," p. 174. Wiley, New York, 1960.
[201] G. M. Badger, "The Chemistry of Heterocyclic Compounds," p. 64. Academic Press, New York, 1961.

compounds; the indole anion was depicted as the resonance hybrid (cf. **433**).[201] A structure of this type could easily explain the substitution behavior observed when the indole Grignard reagents reacted with electrophilic reagents. In 1963 Reinecke *et al.* reported certain spectroscopic evidence that supported the ionic formulation.[15] The



(432) **(433)**

(434) **(435)**

NMR spectrum of indole magnesium bromide in tetrahydrofuran was different from that of indole, but was essentially the same as that obtained from the sodium derivative of indole, a compound in which the nitrogen–metal bond was presumed to be essentially ionic. The similarity of the NMR spectra of these two organometallic indole compounds tended to eliminate the possibility that the essentially covalent N—MgX species **432** made any significant contribution to the overall structure of the indole Grignard reagent. The possibility that the indole magnesium halides existed as either of the C—MgX forms **434** or **435** was also considered unlikely. First signals due to the N—H group could not be detected in either the NMR or the infrared spectra of the indole Grignard reagent; this tended to eliminate structure **434**. The indolenine structure **435** for the indole magnesium halides was also rejected on the grounds that the β-proton resonance observed in the NMR spectrum was not shifted to higher field on formation of the Grignard reagent either from indole or 2-methylindole.[15]

However, the formulation of the indole Grignard reagent as a purely ionic compound appears to be an oversimplification of the picture and is probably incorrect, since several workers have recently described a number of important differences between the behavior of the indole

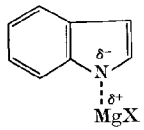
Grignard reagent on the one hand and that of the alkali metal salts of indole on the other. Sebastian reported one significant difference between the NMR spectra of these indole derivatives.[25] An equimolar mixture of indole and indolyl sodium gave the time-averaged spectrum, indicating that rapid exchange was taking place between indole and its sodium derivative. However, the NMR spectrum of a mixture of indole magnesium bromide and indole showed the presence of two distinct sets of resonances due to the presence of both species indicating that no significant exchange was occurring. Temperature had no effect on the NMR spectrum of the mixture.[25] This behavior suggested that the nitrogen–metal bond in the Grignard reagent was of a different character from that in the alkali metal derivatives of indole.

Sebastian also observed that although alkylation of the indole Grignard reagent with methyl iodide in tetrahydrofuran at 23° gave essentially 3-methylindole, variable amounts of 1- and 3-methylindole were obtained on alkylation of the alkali metal salts of indole under similar conditions.[25] Sebastian's results were qualitatively similar to those obtained earlier by Lerner[46] and more recently by Cardillo *et al.*[19] who studied the reaction of a number of organometallic derivatives of indole, including the indole Grignard reagents, with allyl bromide. *N*-Substitution was favored by increasing electropositivity of the cation, i.e., relatively more *N*-substitution was observed in the case of the potassium derivative than in the case of the lithium derivative.[25, 46] Furthermore, factors that tended to facilitate dissociation of the indole salts, such as increasing the polarity of the medium, increased the tendency for substitution to occur at the 1-position (cf. refs. 19, 25, and 46).

Sebastian concluded that all these organometallic indole derivatives were essentially ionic nitrogen–metal species, but with a higher degree of ionic character being present in the nitrogen–alkali metal bond than in the nitrogen–magnesium bond, and that the indol Grignard reagent was best represented by a structure of type shown in formula **436** in which the N—MgX bond has a considerable degree of ionic character but with the possibility of overlap between the nitrogen and magnesium orbitals. He pointed out, however, that his data did not completely eliminate the possibility of an equilibrium of **436** with an ion-pair structure such as **437**.[25]

However, Powers *et al.* concluded, as a result of their investigations of the protonation of the indole Grignard reagent,[17, 192] that in ether

solution, at least, the N—MgX bond of the indole Grignard reagent has a considerable covalent character.[17] In tetrahydrofuran, however, the stronger basicity of this ether, which would coordinate more strongly with the magnesium, would increase the ionic character of the N—MgX bond.[17]



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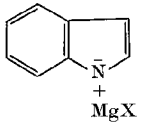

(437)

By virtue of their extensive studies on the interaction of β-dimethylaminoalkyl halides (see Section III, B, 6, b) with some organometallic derivatives of indole, including the indole Grignard reagents, Ganellin and Ridley came to conclusions not too dissimilar to those of Sebastian[25] and Powers *et al.*[17] These workers were able to exclude the possibility of a C—MgX species and concluded that the indole Grignard reagents are essentially N—MgX species in which the N—MgX bond in the indole magnesium halides is formally covalent but is polarized to induce partial anionic character in the indole nucleus, with the consequent increase in electron density at the 3-position, which would facilitate electrophilic substitution at that position.

Foti and Ruff have also reported recently that infrared spectroscopic studies indicate that the magnesium function in indole magnesium iodide is associated with the nitrogen atom of the indole nucleus and not the carbon atom in the 3-position.[202]

Some recent studies have underlined the effect that certain physical properties of the reaction medium have in governing the nature and yields of the products obtained when indole Grignard reagents react with alkyl or alkynyl halides. Such factors include the basicity and dielectric constant of the medium and its ability to solvate any of the reacting species.[18, 19]

In conclusion it appears that the indole magnesium halides are essentially N—MgX species, with the degree of ionic character of the N—MgX bond being markedly affected by external factors, such as

[202] A. Foti and F. Ruff, *Magy. Kem. Folyoirat* **73**, 91 (1967); *Chem. Abstr.* **67**, 11386 (1967).

the polarity of the medium. However, there are still several questions concerning the structure and reactivity of the indole Grignard reagents which are not fully answered by the aforementioned model.

ACKNOWLEDGMENTS

The authors wish to express their thanks to Drs. C. R. Ganellin and J. C. Powers for critically reading the manuscript and to Drs. C. R. Ganellin, A. H. Jackson, and J. C. Powers for giving them to access to some of their results, which were unpublished at the time the manuscript was prepared.

Isoindoles

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I. Introduction

Isoindole (**1**) and its analogs, isobenzofuran (**2**) and isothianaphthene (**3**), have attracted considerable theoretical and synthetic interest.[1,2] Of the parent heterocycles, only isothianaphthene (**3**) has proved sufficiently stable for isolation,[3,4] although both (**1**)[5] and (**2**)[6] have been detected as transient species, and it seems likely that a more complete characterization will be forthcoming with improved experimental techniques. This review is concerned with the chemistry of

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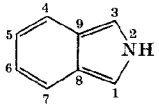
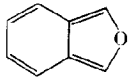
[1] R. C. Elderfield, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. II, p. 68, 162. Wiley, New York, 1951.
[2] R. C. Elderfield and T. N. Dodd, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. III, p. 275. Wiley, New York, 1952.
[3] R. Meyer, H. Kleinert, S. Richter, and K. Gewald, *J. Prakt. Chem.* **20**, 244 (1963).
[4] M. P. Cava and N. M. Pollack, *J. Am. Chem. Soc.* **88**, 4112 (1966).
[5] R. Kreher and J. Seubert, *Z. Naturforsch.* **20b**, 75 (1966).
[6] L. F. Fieser and M. J. Haddadin, *J. Am. Chem. Soc.* **86**, 2081 (1964).

isoindoles and with isoindolenines, e.g., (4) (1*H*-isoindoles), where there is the possibility of tautomerism with, or rearrangement to, the isoindole system. The only review extant on the subject of isoindoles[2] was published, coincidentally, at the time of the first reported preparation of a derivative of this heterocycle and serves to emphasize the lack of success that accompanied early attempts at the synthesis of isoindoles. In spite of (or, perhaps, because of) these early difficulties with synthesis, a good deal of speculation concerning the properties of this system accumulated, ranging from predictions that isoindoles would be too unstable for isolation to calculations which accorded the heterocycle a degree of stabilization comparable with that of indole. With the former assertion refuted, it is now more clearly apparent why isoindoles remained unknown for so long, and some of the factors relevant to this feature of isoindole chemistry are discussed below. Many questions surrounding this interesting heterocyclic system remain unanswered however, and these will undoubtedly serve as a basis for further research.



(1)



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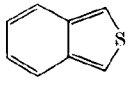

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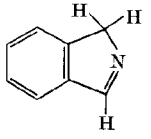


(4)

II. Theoretical Aspects

In a formal sense, isoindole can be regarded as a 10π electron system and, as such, complies with the Hückel $(4n+2)$ rule for aromatic stabilization,[7] with the usual implicit assumption that the crossing bond (8, 9 in **1**) represents a relatively small perturbation of the monocyclic, conjugated system.[8] The question in more explicit terms is whether isoindole possesses aromatic stabilization in excess of that exhibited by pyrrole.

[7] E. Hückel, *Z. Physik* **70**, 204 (1931).
[8] J. R. Platt, *J. Chem. Phys.* **22**, 1448 (1954).

Several calculations of the electronic structure of isoindoles have been published,[9-12] and the distribution of charge density around the isoindole nucleus calculated by these methods is summarized in Table I. A common prediction of the calculations, which are based on the LCAO–MO method[9, 10, 12] or the "frontier electron concept," is the relatively high electron density to be found at position 1, and the expectation, therefore, is that electrophilic substitution on carbon

TABLE I

CALCULATED CHARGE DENSITIES FOR ISOINDOLE

Position					
1	2(*N*)	4	5	8	Ref.
1.185	1.628	1.098	1.052	0.851	9[a]
1.116	1.651	1.008	1.018	1.033	10[b]
0.589	0.000	0.225	0.134	0.051	11[c]
1.112	1.502	1.016	1.041	1.081	12[d]

[a] Parameters: Coulomb integral, $\alpha_N = \alpha$; C–N exchange integral $= 0.55\beta$.
[b] Parameters: $\alpha_N = \alpha + 2\beta$; $\alpha_1 = \alpha + \frac{1}{4}\beta$ (carbon bonded to nitrogen); C–N exchange integral $= \beta$.
[c] Electron density of electron pair in highest occupied molecular orbital. Parameters: $\alpha_N = \alpha + \beta$; C–N exchange integral $= \beta$.
[d] Parameters: $\alpha_N = \alpha + \beta$; C–N exchange integral $= 0.9\beta$.

will occur most readily at this position. There are, however, discrepancies with regard to the relative charge densities at positions 4 and 5, with Dewar[9] and Fukui *et al.*[11] calculating higher density at the 4-position, whereas Longuet-Higgins and Coulson[10] predict the reverse. The semiempirical calculations of Dewar[9] and Polansky and Derflinger[12] estimate a substantial degree of resonance stabilization for isoindole with a value of about 56 kcal/mole. This is significantly larger than the calculated (17–31 kcal/mole[13]) and experimentally

[9] M. J. S. Dewar, *Trans. Faraday Soc.* **42**, 764 (1946).
[10] H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.* **43**, 87 (1947).
[11] K. Fukui, T. Yonezawa, C. Nagata, and H. Shingu, *J. Chem. Phys.* **22**, 1433 (1954).
[12] O. E. Polansky and G. Derflinger, *Monatsh. Chem.* **92**, 1114 (1961).
[13] H. Zimmermann and H. Geisenfelder, *Z. Elektrochem.* **65**, 368 (1961).

determined (21–25 kcal/mole[14]) values for pyrrole and is close to that attributed to indole.[9, 13, 14] Dewar[9] therefore concludes that "isoindole should be definitely aromatic."

According to a molecular orbital calculation of Veber and Lwowski,[15] isoindole should be favored over its tautomer, isoindolenine, by about 8 kcal/mole. However, the calculated electronic distribution is markedly different in the two cases, particularly at position 1, and it is to be expected that the nature and pattern of substituents will play an important role in determining the position of tautomeric equilibrium between these two species.

III. Synthesis of Isoindoles

A. Syntheses from Isoindolines

Isoindolines comprise a group of well-characterized and easily synthesized substances,[2] and being at the next stable reduction state below that of isoindoles, they constitute suitable precursors for synthesis of the latter. In principle, either oxidation or elimination from isoindolines should lead to isoindoles; however, in view of the susceptibility of isoindoles to further oxidation, elimination has been preferred, and in all cases reported the leaving group has been placed on nitrogen rather than carbon.

1. *Isoindolinium Salts*

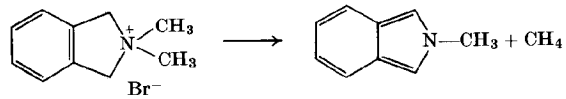
The first clearly authenticated preparation of an isoindole was reported by Wittig *et al.*[16] in 1951. It was found that elimination from isoindolinium bromides and iodides with bases such as aryl- and alkyllithium afforded 2-substituted isoindoles in variable yields. For instance, 2,2-dimethylisoindolinium bromide (**5**) on treatment with one equivalent of phenyllithium in ether under nitrogen, evolved methane and gave 2-methylisoindole (**6**) in 74% yield. With methyllithium as base, a slightly lower yield was obtained.

Di-*o*-xylyleneammonium bromide (**7**) gave only an 8% yield of 2-*o*-tolylisoindole (**8**) with phenyllithium, although the yield was

[14] G. W. Wheland, "Resonance in Organic Chemistry," p. 99. Wiley, New York, 1955.

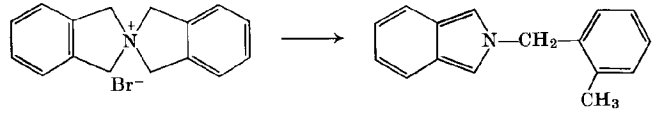
[15] D. F. Veber and W. Lwowski, *J. Am. Chem. Soc.* **86**, 4152 (1964).

[16] G. Wittig, H. Tenhaeff, W. Schoch, and G. Koenig, *Ann. Chem.* **572**, 1 (1951).



(5) (6)

improved slightly when aqueous silver oxide was used and the resulting hydroxide pyrolyzed at 170°.



(7) (8)

In the case of elimination from (**9**), isoindole formation competes with 1,2-migration of the benzyl group (Stevens rearrangement[17]), which gives 1-benzyl-2-methylisoindoline (**10**), and also with migration

TABLE II

Rearrangement and Elimination Products from 2-Benzyl-2-methylisoindolinium Bromide with Base[a]

Base	Solvent	Temp. (°C)	Yield (%) (10)	(11)	(6)
NH_2^-	NH_3	−33	—	87	—
$C_6H_5^-$	$(C_2H_5)_2O$	20–30	—	69	—
$C_2H_5O^-$	C_2H_5OH	ca. 80	44	—	15
$C_6H_5^-$	$(n\text{-}C_4H_9)_2O$	120	41	—	—
OH^-	—	ca. 180	33	—	40

[a] Data of G. Wittig and H. Streib, *Ann. Chem.* **584**, 1 (1953).

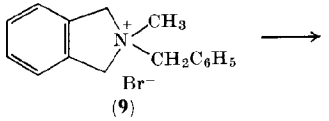
accompanied by attack at the *ortho* position of the phenyl ring (Sommelet rearrangement[18]) which gives 1-*o*-tolyl-2-methylisoindoline (**11**).[19] From a study of product ratios under various reaction conditions (Table II), it may be concluded[19] that low temperatures favor

[17] T. S. Stevens, E. M. Creighton, A. B. Gordon, and M. MacNicol, *J. Chem. Soc.* p. 3193 (1928).

[18] M. Sommelet, *Compt. Rend.* **205**, 56 (1937).

[19] G. Wittig and H. Streib, *Ann. Chem.* **584**, 1 (1953).

Sommelet rearrangement, intermediate temperatures favor Stevens rearrangement,[20] and high temperatures promote elimination to form isoindoles. Treatment of 2-methyl-2-*o*-tolylmethylisoindolinium



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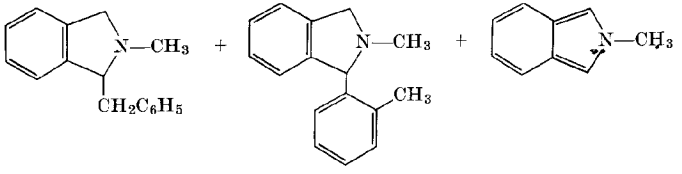
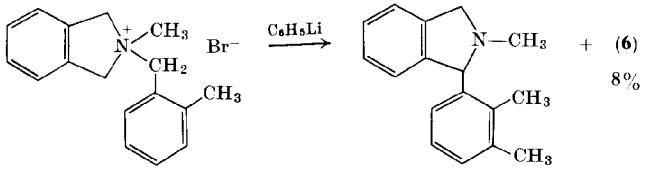
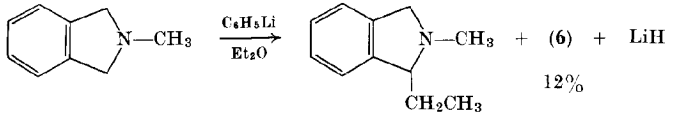


(10) (11) (6)

bromide (**12**) with phenyllithium gives predominantly the Sommelet rearrangement product (**13**), with only a low yield of (**6**).[19] 2-Methylisoindole (**6**) can also be obtained by the reaction of 2-methylisoindoline (**14**) with phenyllithium, although the major product (**15**) is apparently derived from reaction with the solvent.[19]



(12) (13) 54% (6) 8%

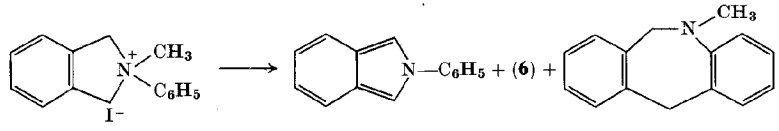


(14) (15) 40% (6) 12% LiH

The reaction of 2-methyl-2-phenylisoindolinium iodide (**16**) with potassium amide as the base, affords both 2-phenyl- (**17**) and 2-methylisoindole (**6**), together with the azadibenzocycloheptadiene (**18**).[21]

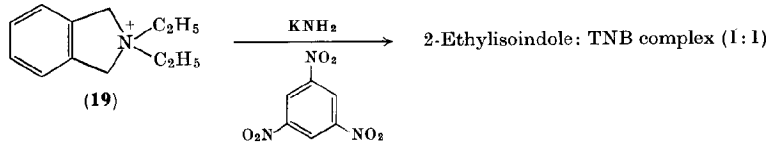
[20] S. W. Kantor and C. R. Hauser, *J. Am. Chem. Soc.* **73**, 4122 (1951).

[21] G. Wittig, G. Closs, and F. Mindermann, *Ann. Chem.* **594**, 89 (1955). For a recent study of the mechanism of formation of (**18**), see P. P. Gaspar and T. C. Carpenter, *Angew. Chem. Intern. Ed. English* **6**, 559 (1967).



(16) (17) (18)

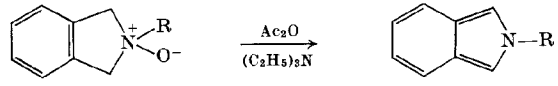
2,2-Diethylisoindolinium iodide (**19**) is reported to give 2-ethylisoindole with potassium amide[22]; the isoindole was not isolated as such, however, but was characterized as its complex with 1,3,5-trinitrobenzene (TNB).



(19) 2-Ethylisoindole: TNB complex (1:1)

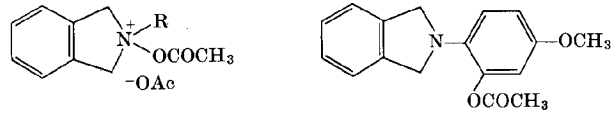
2. *Isoindoline N-Oxides*

Elimination from *N*-oxides of substituted isoindolines provides an exceptionally facile synthesis of the isoindole system. Kreher and Seubert found that treatment of the oxides of both 2-alkyl-[23] and 2-arylisoindolines[24] with acetic anhydride at 0° to −10° afforded



(20)

R = C_2H_5, *n*-C_4H_9, C_6H_5, $C_6H_5CH_2$



(21) (22)

2-substituted isoindoles in up to 70% yield. The initial reaction presumably occurs between the isoindoline oxide (**20**) and acetic anhydride to give the acetoxyisoindolinium acetate (**21**), which then undergoes an elimination reaction. The product (**22**), isolated from

[22] J. Thesing, W. Schaefer, and D. Melchior, *Ann. Chem.* **671**, 119 (1964).

[23] R. Kreher and J. Seubert, *Angew. Chem. Intern. Ed. English* **3**, 639 (1964).

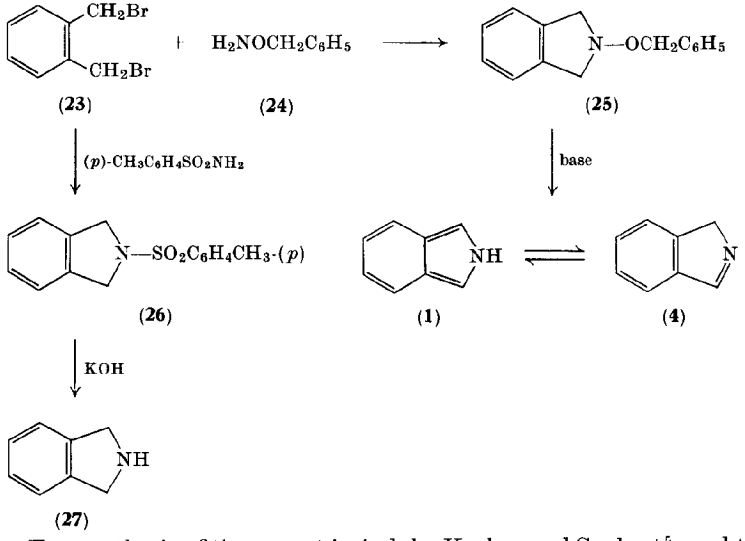
[24] R. Kreher and J. Seubert, *Angew. Chem. Intern. Ed. English* **5**, 967 (1966).

the *N*-oxide of 2-*p*-methoxyphenylisoindoline under these conditions, is apparently derived from a Fries rearrangement[25] of an intermediate of this type (**21**, R = *p*-methoxyphenyl).

Pyrolytic elimination from isoindoline *N*-oxides also affords isoindoles,[22] but yields were found to be generally lower than those obtained by Kreher and Seubert's procedure.[23, 24] The considerable amount of polymeric material formed in the pyrolytic reaction makes isolation of the isoindole difficult, but a convenient method for separation of the product was found utilizing complex formation with 1,3,5-trinitrobenzene.

3. *2-Substituted Isoindolines*

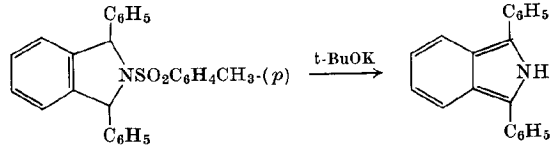
In contrast to isoindolinium salts and *N*-oxides of isoindolines, successful elimination from simple 2-substituted isoindolines has been realized in only two cases. One of these, however, was the synthesis of isoindole itself, and it seems likely that this method is particularly well suited to the preparation of other sensitive isoindoles.



For synthesis of the parent isoindole, Kreher and Seubert[5] used the condensation of the *o*-xylene dibromide (**23**) with *O*-benzylhydroxylamine (**24**) to give 2-benzyloxyisoindoline (**25**). Elimination occurred

[25] A. H. Blatt, *Chem. Rev.* **27**, 429 (1940).

with potassium *t*-butoxide in dimethyl sulfoxide at 25° to give a solution containing isoindole (**1**) in equilibrium with its tautomer, isoindolenine (**4**). Although no spectral observations could be made, the presence of isoindole was inferred from the formation of Diels–Alder adducts with maleic anhydride and *N*-phenylmaleimide (see Section IV, D). An approach to isoindole, conceived originally by Fenton and Ingold,[26] involved treatment of 2-*p*-toluenesulfonylisoindoline (**26**) with potassium hydroxide. The only product characterized, however, was isoindoline (**27**), presumably formed by hydrolysis of the sulfonamide. An elimination route has been applied by

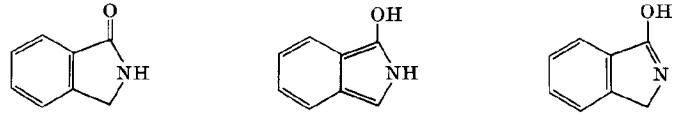


(**28**) (**29**)

Emmett *et al.*[27] in the preparation of 1,3-diphenylisoindole (**29**) from the *p*-toluenesulfonyl derivative (**28**).

B. Syntheses from Phthalimidines

Syntheses of phthalimidines (e.g., **30**) do not in themselves constitute syntheses of isoindoles or isoindolenines, since the lactam from shows no tendency to tautomerize, as discerned from spectroscopic evidence, to lactim forms (**31** and **32**).[28] However, phthalimidines are



(**30**) (**31**) (**32**)

readily converted into isoindoles by reaction with alkyl and aryl lithium compounds and with Grignard reagents (Table III).[19, 21, 29–31]

[26] G. W. Fenton and C. K. Ingold, *J. Chem. Soc.* p. 3295 (1928).
[27] J. C Emmett, D. F. Veber, and W. Lwowski, *Chem. Commun.* p. 272 (1965).
[28] A. E. Kellie, D. G. O'Sullivan, and P. W. Sadler, *J. Chem. Soc.* p. 3809 (1956).
[29] W. Theilacker and H. Kalenda, *Ann. Chem.* **584**, 87 (1953).
[30] W. Theilacker and W. Schmidt, *Ann. Chem.* **597**, 95 (1955).
[31] W. Theilacker and W. Schmidt, *Ann. Chem.* **605**, 43 (1957).

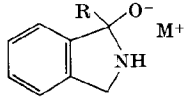
The intermediate alkylation product (**33**) undergoes facile elimination. In one instance a hydroxyisoindoline (**34**) was isolated and subsequently dehydrated to the corresponding isoindole.[29] The phthalimidine route has been used to prepare mainly 1,2-disubstituted

TABLE III

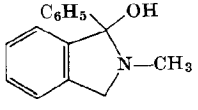
ISOINDOLES PREPARED FROM PHTHALIMIDINES

Isoindole	Reagent	Conditions	Yield (%)	Ref.
1-Benzyl-2-methyl	$C_6H_5CH_2Li$	Ether	54	19
1-Phenyl-2-methyl	C_6H_5Li	Ether, reflux	79	29
1-Phenyl-2-methyl	C_6H_5MgBr	1. Anisole, 140°–150° 2. Ammonium acetate	34	29
1-Ethyl-2-methyl	C_2H_5MgBr	Anisole, 70°	42	29
1-Butyl-2-methyl	n-C_4H_9Li	Benzene, 40°	50	29
2-Methyl	$LiAlH_4$	Ether, 80° (sealed)	68	21
2-Phenyl	$LiAlH_4$	Ether, 100° (sealed)	29	21
1-Methyl-2-phenyl	CH_3Li	Ether	65	21
1,3-Diphenyl-2-methyl	C_6H_5Li	Ether, benzene	93	30
1,2,3-Triphenyl	C_6H_5Li	Dioxane, reflux	86	31

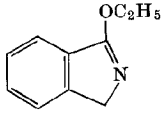
isoindoles. 2-Substituted isoindoles (e.g., **6** and **17**) can be obtained by reduction of the corresponding 2-substituted phthalimidines with lithium aluminum hydride at elevated temperatures.[21]



(**33**)



(**34**)



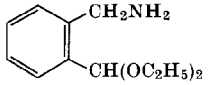
(**35**)

The reaction between phthalimidine (**30**) and triethyloxonium fluoroborate is reported to give the fluoroborate salt of 1-ethoxyisoindolenine, from which the free base (**35**) can be liberated.[32] The isoindolenine (**35**) apparently shows no detectable tautomerism with the isoindole form (see Section IV,A).

[32] S. Petersen and E. Tietze, *Ann. Chem.* **623**, 166 (1959).

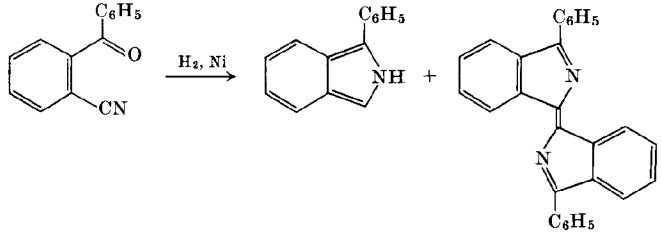
C. Syntheses from Ortho-Disubstituted Benzenes

Attempts to prepare isoindolenine (**4**) by pyrolytic or acid-catalyzed elimination from the aminoacetal (**36**). proved fruitless, the only



(**36**)

products being polymeric substances.[33] However, several successful isoindole syntheses have been realized from ortho-disubstituted benzene derivatives, using other procedures. For instance, catalytic reduction over Raney nickel of *o*-cyanobenzophenone (**37**) gave 1-phenylisoindole (**38**), accompanied by the oxidative coupling product (**39**).[34] The yield of isoindole in this reaction is critically dependent on the activity of the Raney nickel.



(**37**) (**38**) (**39**)

An ingenious synthesis of 1-arylisoindoles has been developed by Veber and Lwowski, based upon the reaction of an *o*-phthalimidomethylbenzophenone (**41**, R = aryl) with hydrazine (Table IV).[15,35] The benzophenone is prepared by a Friedel–Crafts reaction with *o*-phthalimidomethylbenzoyl chloride (**40**). The mechanism of isoindole formation can be represented schematically by a sequence involving attack by hydrazine at the imide to give the ring-opened hydrazide (**42**), followed by cyclization to phthalazine-1,4-dione (**44**) with displacement of the *o*-aminomethylbenzophenone (**43**). Intramolecular condensation of the latter can lead, via the isoindolenine

[33] J. Bornstein, S. F. Bedell, P. E. Drummond, and C. L. Kosloski, *J. Am. Chem. Soc.* **78**, 83 (1956).

[34] R. Kreher and J. Seubert, *Tetrahedron Letters* p. 3015 (1966).

[35] D. F. Veber and W. Lwowski, *J. Am. Chem. Soc.* **85**, 646 (1963).

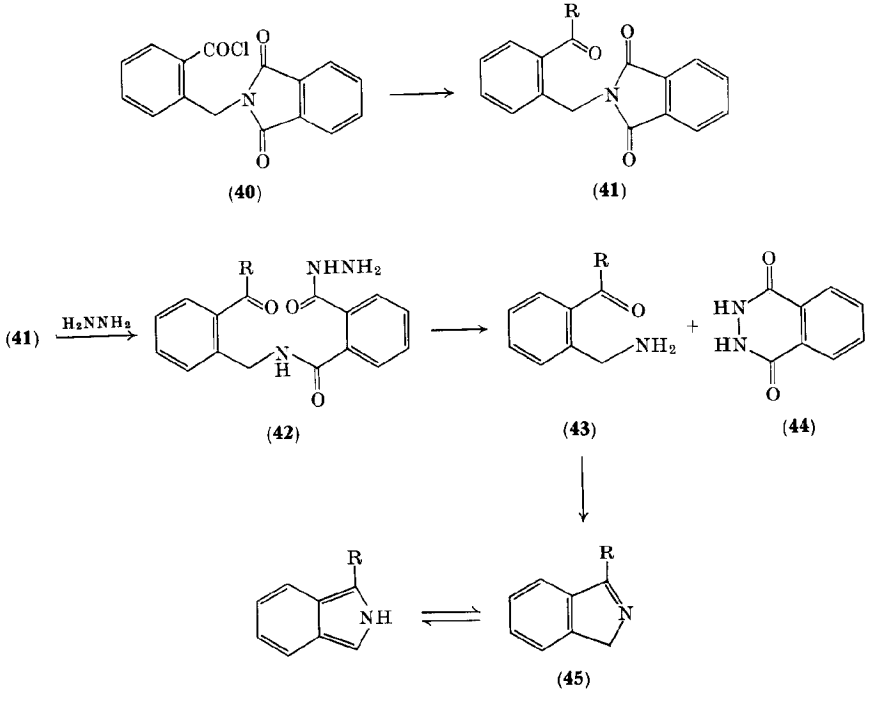
TABLE IV

1-ARYLISOINDOLES PREPARED FROM PHTHALIMIDOBENZOPHENONES[a]

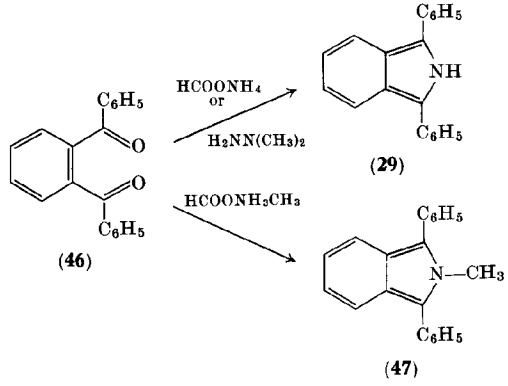
Isoindole	Yield (%)
1-Phenyl	80
1-*p*-Methoxyphenyl	53
1-*p*-Dimethylaminophenyl	50

[a] Data of D. F. Veber and W. Lwowski, *J. Am. Chem. Soc.* **86**, 4152 (1964).

(**45**), to a 1-substituted isoindole. Isoindoles prepared in this way were the first to be obtained without substituents on nitrogen and proved to be appreciably less stable than their 2-substituted counterparts. An attempt to prepare isoindole itself by this route was unsuccessful.



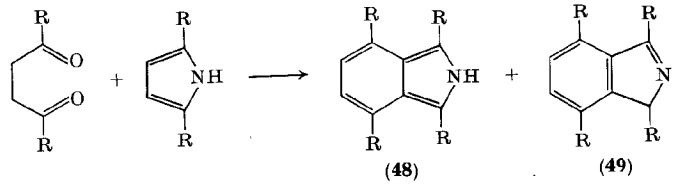
1,3-Diphenylisoindole (**29**) can be prepared by a modified Leuckart reaction[36] of *o*-dibenzoylbenzene (**46**), using an ammonium salt of formic acid[27, 37]: the process is essentially a reductive alkylation of ammonia, accompanied by cyclization, and leads to **29** in 44% yield with ammonium formate, and **47** in 28% yield with methylammonium formate. 1,3-Diphenylisoindole (**29**) can also be obtained in good yield by the reaction of **46** with 1,1-dimethylhydrazine.[37]



D. CONDENSATION OF 1,4-DIKETONES WITH AMINES AND PYRROLES

A method for the synthesis of certain substituted isoindoles has been developed by Norton[38] and by Fletcher[39] using the acid-catalyzed condensation of a 1,4-diketone with substituted pyrroles (Table V). 2,5-Disubstituted pyrroles give tautomeric mixtures of isoindoles and isoindolenines (**48** and **49**),[39] whereas 1,2,5-trisubstituted pyrroles give the corresponding 2-substituted isoindoles.[38] In certain cases the 2-substituted isoindoles can be obtained by allowing the diketone to condense directly with a primary amine in the presence of a strong acid at elevated temperatures[38]; the initially formed pyrrole undergoes a further reaction with the diketone under these conditions to yield the isoindole. The greater sensitivity of isoindoles

[36] M. C. Moore, *in* "Organic Reactions" (R. Adams, ed.), Vol. V, p. 301. Wiley, New York, 1949.
[37] J. C. Emmett and W. Lwowski, *Tetrahedron* **22**, 1011 (1966).
[38] F. H. Norton, U.S. Patent 3,007,939 (1961); *Chem. Abstr.* **56**, 7281 (1962).
[39] H. Fletcher, *Tetrahedron* **22**, 2481 (1966).



(48) (49)

lacking a substituent on nitrogen necessitates a careful choice of reaction conditions for their preparation by this route. Chloroacetic

TABLE V

TYPICAL ISOINDOLES PREPARED FROM 1,4-DIKETONES

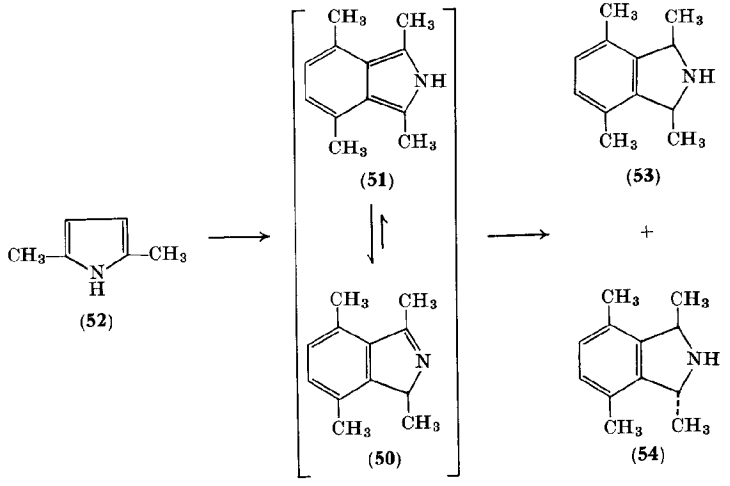
Isoindole	Reagents	Conditions	Yield (%)	Ref.
1,3,4,7-Tetraphenyl	1,2-Dibenzoylethane, 2,5-diphenylpyrrole	Trichloroacetic acid, hexane, reflux	39	38
1,3-Diphenyl-4,7-dimethyl	2,5-Hexanedione, 2,5-diphenylpyrrole	*p*-Toluenesulfonic acid, toluene, reflux	32	38
1,3,4,7-Tetramethyl-2-phenyl	2,5-Hexanedione, aniline	150°–160°, sealed	—	39

acid in hexane or *p*-toluenesulfonic acid in toluene appears to be an effective catalyst for the condensation of 2,5-disubstituted pyrroles with 1,4-diketones.

1,3,4,7-Tetramethylisoindolenine (**50**) is obtained as an unstable, crystalline solid from the reaction of 2,5-hexanedione with 2,5-dimethylpyrrole in the presence of sulfuric acid.[39] Treatment of the same diketone with ammonium sulfate also affords this isoindolenine. NMR measurements in deuteriochloroform indicate that a small amount of 1,3,4,7-tetramethylisoindole (**51**) is present in equilibrium with the isoindolenine. This same isoindole was postulated as an intermediate in the reductive self-condensation of 2,5-dimethylpyrrole (**52**) which affords a mixture of *cis*- and *trans*-1,3,4,7-tetramethylisoindolines (**53** and **54**).[40,41] Hydrolytic opening of the

[40] R. Bonnett and J. D. White, *Proc. Chem. Soc.* p. 119 (1961).
[41] R. Bonnett and J. D. White, *J. Chem. Soc.* p. 1648 (1963).

pyrrole to give 2,5-hexanedione was demonstrated, and subsequent condensation presumably occurs in the manner described by Fletcher.[39] Careful treatment of 2,5-dimethylpyrrole with acid has, in fact, been shown to produce the isoindole–isoindolenine mixture (**50** and **51**).[42] Reduction of 1,3,4,7-tetramethylisoindolenine by catalytic means or with a metal-acid system gives the corresponding isoindolines (**53** and **54**).

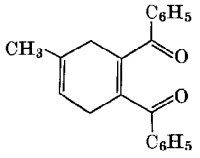


(52) (51) (50) (53) (54)

A useful and possibly more general alternative to the Lwowski synthesis[27,37] of 1,3-diphenylisoindoles involves condensation of a 1,2-dibenzoyl-1,4-cyclohexadiene (e.g., **55**) with ammonia or a primary amine.[43] Cyclohexadiene derivatives of this type are easily prepared by Diels–Alder addition of a 1,3-diene to dibenzoylacetylene,[44,45] and these adducts lead directly, and in high yield, to the corresponding isoindoles (**56**). The reaction is closely related to the well-known synthesis of pyrroles by condensation of 1,4-diketones with ammonia. 4,7-Dihydro- and 4,5,6,7-tetrahydroisoindoles (**57** and **58**) have been

[42] C. O. Bender and R. Bonnett, *Chem. Commun.* p. 198 (1966).
[43] J. D. White and M. E. Mann, unpublished results.
[44] G. Dupont and J. Germain, *Compt. Rend.* **223**, 743 (1946).
[45] G. Dupont and J. Germain, *Bull. Soc. Chim. France* p. 526 (1947).

prepared by an analogous condensation of 1,2-diacetylcyclohex-4-ene and 1,2-diacetylcyclohexane with ammonia.[46, 47]



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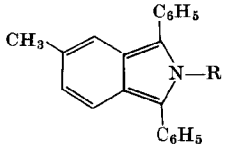

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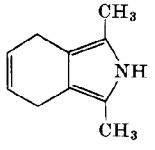

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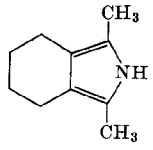
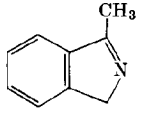


(58)

E. Other Reactions and Rearrangements Leading to Isoindoles

Several novel reactions and rearrangements giving isoindoles as stable end products have been reported. For certain isoindoles, such processes afford an efficient preparative route to a specific derivative.

An early claim by Gabriel and Neumann[48] to have synthesized 1-methylisoindolenine (**59**) from the diazanaphthalene (**60**) has been shown to be in error,[49] the actual product being 1-methylisoindoline (**61**). Several synthetic routes to 1,3,3-trisubstituted isoindolenines



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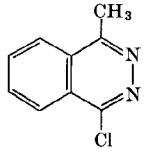

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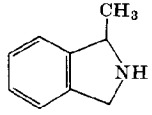
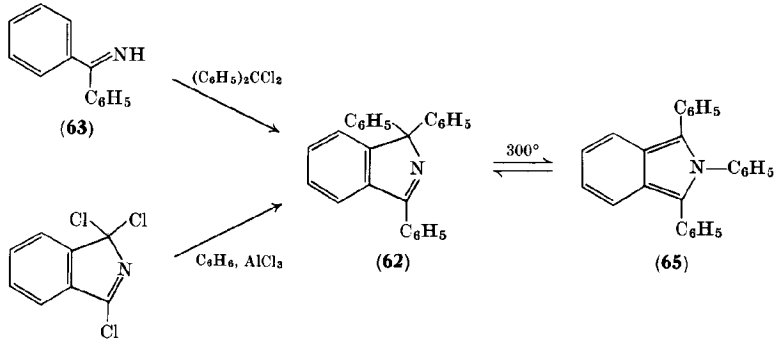


(61)

[46] G. O. Schenck, *Chem. Ber.* **80**, 226 (1947).
[47] M. Fetizon, H. Fritel, J. Levisalles, and P. Baranger, *Compt. Rend.* **242**, 2014 (1956).
[48] S. Gabriel and A. Neumann, *Ber. Deut. Chem. Ges.* **26**, 705 (1893).
[49] R. P. Linstead and E. G. Noble, *J. Chem. Soc.* p. 933 (1937).

have been described,[50–60] and in one case, that of the triphenyl derivative (**62**), rearrangement to an isoindole has been found to occur.[56] At temperatures above 300°, the isoindolenine, which can be prepared from benzophenone imine (**63**) and diphenyldichloromethane or from the trichloroisoindolenine (**64**) by Friedel–Crafts alkylation of benzene, is in equilibrium with 1,2,3-triphenylisoindole (**65**). This

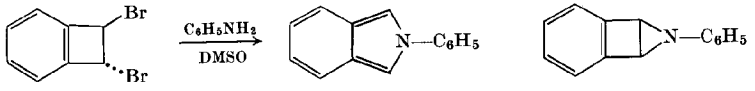


(63) (64) (62) (65)

rearrangement provides the only example in which the isoindole–isoindolenine tautomerism involves a migrating group other than a hydrogen atom.

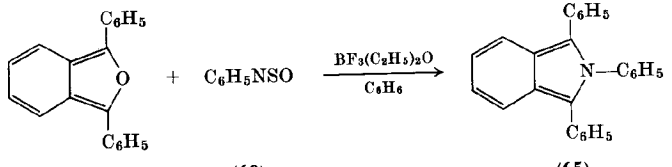
Treatment of *trans*-1,2-dibromobenzocyclobutene (**66**) with aniline in dimethyl sulfoxide (DMSO) is reported to lead to 2-phenylisoindole (**17**) in yields "up to 40%."[24] An interesting possibility in this case is involvement of the isoindole valence tautomer (**67**) as an intermediate.

[50] P. A. Barrett, R. P. Linstead, G. A. P. Tuey, and J. M. Robertson, *J. Chem. Soc.* p. 1809 (1939).
[51] R. Weiss and E. Freund, *Monatsh. Chem.* **45**, 105 (1924).
[52] R. C. Fuson, W. D. Emmons, and R. Tull, *J. Org. Chem.* **16**, 648 (1951).
[53] R. A. Brooks, U.S. Patent 2,980,691 (1961); *Chem. Abstr.* **55**, 19972 (1961).
[54] F. Seidel and O. Bezner, *Ber. Deut. Chem. Ges.* **65**, 1566 (1932).
[55] D. R. Boyd and D. E. Ladhams, *J. Chem. Soc.* p. 2089 (1928).
[56] W. Theilacker, H. J. Bluhm, W. Heitmann, H. Kalenda, and H. J. Meyer, *Ann. Chem.* **673**, 96 (1964).
[57] Farbenfabriken Bayer A.-G., British Patent 704,595 (1955); *Chem. Abstr.* **49**, 7001 (1955).
[58] H. P. Kaufmann and L. Fleiter, *Fette, Seifen, Anstrichmittel* **66**, 477 (1964); *Chem. Abstr.* **61**, 14895 (1964).
[59] Farbenfabriken Bayer A.-G., Netherlands Patent Appl. 6,404,971 (1965); *Chem. Abstr.* **62**, 13314 (1965).
[60] W. Theilacker and H. Mohl, *Ann. Chem.* **563**, 99 (1949).

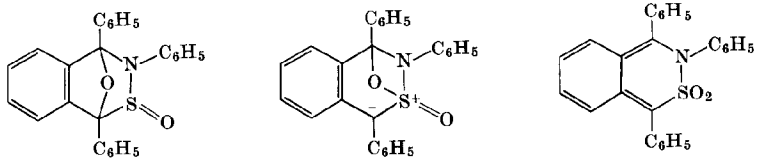


(66) (17) (67)

Cava and Schlessinger have reported the synthesis of 1,2,3-triphenylisoindole (**65**) in 78% yield from 1,3-diphenylisobenzofuran (**68**) by reaction with thionylaniline (**69**) and boron trifluoride.[61] The mechanism proposed for this remarkable transformation involves rearrangement of the adduct (**70**) derived from thionylaniline and the isobenzofuran, to the tricyclic intermediate (**71**). This presumably collapses to the δ-sultam (**72**), which yields the isoindole (**65**) upon extrusion of sulfur dioxide. Loss of sulfur dioxide, both from δ-sultones and unsaturated δ-sultams, is well documented.[62, 63]



(68) (69) (65)

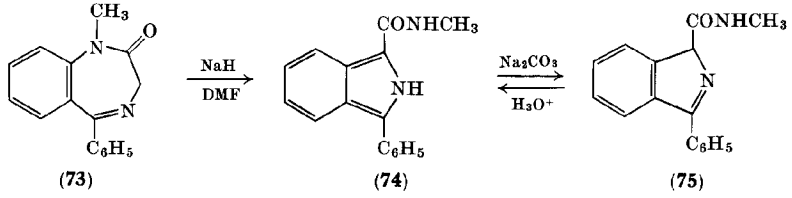


(70) (71) (72)

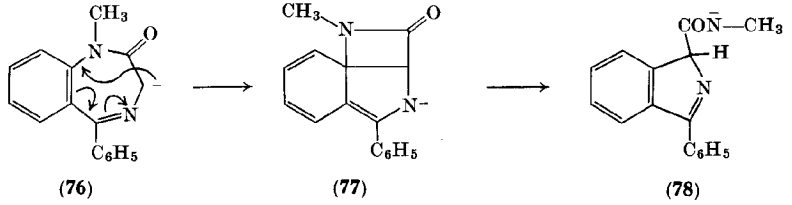
Fryer *et al.* have found that benzodiazepinones rearrange to isoindoles in high yield under a variety of conditions.[64, 65] The benzodiazepinone (**73**), on treatment with sodium hydride in dimethyl formamide (DMF), gave the isoindolecarboxamide (**74**) in better than

[61] M. P. Cava and R. H. Schlessinger, *J. Org. Chem.* **28**, 2464 (1963).
[62] T. Morel and P. E. Verkade, *Rec. Trav. Chim.* **70**, 35 (1951), and references cited.
[63] B. Helferich and W. Klebert, *Ann. Chem.* **657**, 79 (1962).
[64] R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Am. Chem. Soc.* **88**, 3173 (1966).
[65] R. I. Fryer, B. Brust, J. V. Earley, and L. H. Sternbach, *J. Chem. Soc.* **C**, 366 (1967).

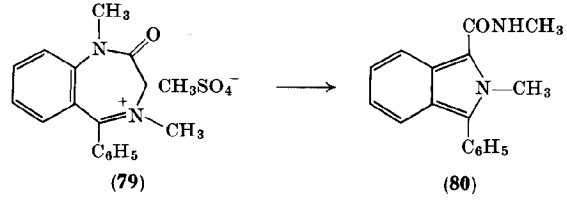
80% yield.[64] Using base catalysts, the isoindole was tautomerized to the isoindolenine form (**75**), which could apparently be reconverted to (**74**). Both the isoindole and isoindolenine were stable, isolable substances in this case—the first instance in which each tautomer has been obtained free of the other. The mechanism postulated for the conversion of (**73**) to (**74**) involves an initial proton abstraction by hydride at the methylene group of the diazepinone nucleus to form the intermediate anion (**76**). Intramolecular nucleophilic displacement can lead to the isoindoleninecarboxamide anion (**78**) via the tricyclic intermediate (**77**), and final protonation accompanied by tautomerization results in **74**. The methosulfate salt (**79**), under the same conditions, rearranges in similar fashion to (**80**).



(73) (74) (75)



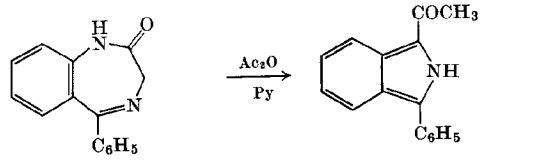
(76) (77) (78)



(79) (80)

1,4-Benzodiazepinones also undergo rearrangement to isoindoles when treated with acetic anhydride and pyridine (Py).[65] The diazepinone (**81**), for instance, gives 1-phenyl-3-acetylisoindole (**82**) under these conditions. The structure of the product was established in this case by comparison with (**82**) prepared by acetylation of 1-phenylisoindole. The rearrangement may be formally represented by a

pathway similar to that outlined above, which would again lead to the isoindolecarboxamide derivative (**74**). Substitution of an acetyl functionality for the amide group might reasonably occur via the *N,N*-diacetyl derivative (**83**) and the intermediate (**84**). It is believed that acetyl isocyanate is evolved in this reaction.



(**81**) (**82**) (**83**) (**84**)

IV. Properties of the Isoindole System

A. Tautomerism

Two independent molecular orbital calculations (HMO method) of delocalization energies for isoindole and isoindolenine tautomers agree that the isoindole form should possess the more resonance stabilization.[15,66] The actual difference calculated for isoindole-isoindolenine is about 8 kcal/mole, but increases in favor of the isoindole with phenyl substitution at position 1 (Table VI).[67] Since isoindole and isoindolenine tautomers have roughly comparable thermodynamic stabilities, the tautomeric process is readily observable by methods such as nuclear magnetic resonance and ultraviolet spectroscopy.

[66] J. Kopecky, J. E. Shields, and J. Bornstein, *Tetrahedron Letters* p. 3669 (1967).

[67] It is of interest that the reversible migration of hydrogen between positions 1 and 2 of this system correspond to a 1,5-sigmatropic shift, a process predicted to be favorable on theoretical grounds [R. B. Woodward and R. Hoffmann, *J. Am. Chem. Soc.* **87**, 2511 (1965)] and known to occur with exceptional facility (R. B. Woodward *in* "Aromaticity," Spec. Publ. No. 21, p. 217. The Chemical Society, London, 1967).

TABLE VI

Calculated Delocalization Energies for Isoindoles and Isoindolenines[a]

Isoindole/isoindolenine	D.E. (units of β)
Isoindole	2.82
Isoindolenine	2.44
1-Phenylisoindole	5.28
1-Phenylisoindolenine	4.84
Benz[*f*]isoindole	4.42
Benz[*f*]isoindolenine	4.12

[a] Data from J. Kopecky, J. E. Shields, and J. Bornstein, *Tetrahedron Letters* p. 3669 (1967).

The isoindole–isoindolenine equilibrium has been studied quantitatively only in the case of certain 1-arylisoindoles.[15] Although two structurally different isoindolenines are possible, only that with the carbon–nitrogen double bond conjugated with both aromatic rings was observed. Investigation of the isoindole–isoindolenine ratios for three compounds by NMR and ultraviolet spectroscopy indicated a

TABLE VII

Effect of Substituents on the Isoindole–Isoindolenine Equilibrium[a]

Substituent	Isoindole[b] (%)	Equilibrium constant	ΔF_{302} (kcal/mole)
1-Phenyl	91	10.1	1.38
1-*p*-Methoxyphenyl[c]	69	2.23	0.48
1-*p*-Dimethylaminophenyl[d]	50	1.00	0.00

[a] Data of D. F. Veber and W. Lwowski, *J. Am. Chem. Soc.* **86**, 4152 (1964).

[b] Determined by NMR in $CDCl_3$ solution.

[c] A study of the solvent dependence of the equilibrium for this substituent gave the following results: benzene (84% isoindole), acetonitrile (87%), ethanol (90%), and ether (99%).

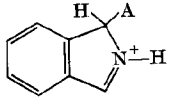
[d] Addition of pyridine to a benzene solution of this derivative was found to convert it from 80% of the isoindole tautomer to 100% isoindole.

marked dependence on the nature of the substituent as shown in Table VII. The relative positions of equilibrium of the three compounds in the same solvent correlates with the electronegativity of the substituent, the more highly electron-donating substituent increasing the proportion of the isoindolenine form. This finding is consistent with calculations attributing a lower π-electron density at position 1 for isoindolenine than for isoindole (see Table I). Further evidence that electron-donating substituents stabilize the isoindolenine is provided by the observation of Petersen and Tietze that treatment of phthalimidine with triethyloxonium fluoroborate gives 1-ethoxyisoindolenine, with no detectable formation of the isoindole.[32]

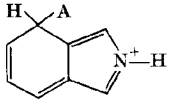
As expected, alkyl substitution also favors the isoindolenine, although accurate quantitative evaluation of proportions of tautomers is made difficult here by the instability of these derivatives.[42] NMR measurements of 1,3,4,7-tetramethylisoindolenine indicate that this tautomer predominates over the corresponding isoindole by about 8:1.[39]

B. Electrophilic Substitution

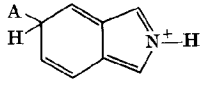
It is apparent from simple valence bond considerations as well as from calculations of π-electron density,[9-12] that isoindoles should be most susceptible to electrophilic attack at carbon 1. This preference is most clearly evident when the intermediate cations (**85–87**) from electrophilic attack (by A^+) at positions 1, 4, and 5 are considered. The benzenoid resonance of **85** is the decisive factor in favoring this intermediate over its competitors.



(85)



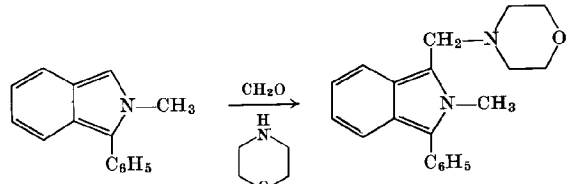
(86)



(87)

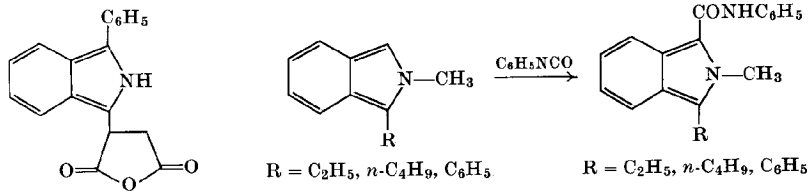
Experimental evidence substantiates this view. Protonation of isoindoles converts them reversibly into isoindolenium salts, as judged by changes in NMR[42] and ultraviolet spectra.[43] Isoindoles having an open position alpha to nitrogen give a positive Ehrlich reaction, whereas 1,3-disubstituted isoindoles give a negative response. Isoindoles can also undergo a Mannich condensation at the 1- or

3-position; 1-phenyl-2-methylisoindole (**88**) reacts with paraformaldehyde and morpholine to give the morpholinomethyl derivative (**89**).[29]



(88) (89)

In certain cases where a Diels–Alder addition might have been anticipated, substitution of the isoindole is apparently preferred. For example, 1-phenylisoindole (**38**) with maleic anhydride gives the succinic anhydride derivative (**90**).[19] In this respect the chemistry of isoindoles resembles that of pyrroles which also react with dienophiles to give, with a few exceptions,[68-70] products derived from additive substitution.[71,72] The structures of the products from phenylisocyanate and certain 1-substituted 2-methylisoindoles (**91**), which were initially thought to be Diels–Alder adducts,[29] have been found instead to be isoindoleamides (**92**), the products of substitution at the open 3-position.[30] 1,2,3-Trisubstituted isoindoles do not react with phenyl isocyanate. Acetylation of 1-phenylisoindole (**38**) can be

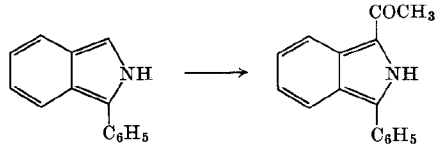


(90) (91) (92)

effected under mild conditions using acetic anhydride in pyridine to give exclusively the 3-acetyl derivative (**93**). In another procedure, (**38**) is allowed to react with a Grignard reagent to give a dark green

[68] L. Mandell and W. A. Blanchard, *J. Am. Chem. Soc.* **79**, 6198 (1957).
[69] G. Wittig and W. Behnisch, *Chem. Ber.* **91**, 2358 (1958).
[70] R. M. Acheson and J. M. Vernon, *J. Chem. Soc.* p. 457 (1961).
[71] O. Diels and K. Alder, *Ann. Chem.* **490**, 267 (1931).
[72] O. Diels and K. Alder, *Ann. Chem.* **498**, 1 (1932).

solution of the isoindole–magnesium complex, which affords (**93**) on treatment with acetyl chloride.[65]



(**38**) (**93**)

C. Reduction–Oxidation

Redox measurements[73] (see Table VIII) on several isoindole derivatives indicate that this system should be particularly susceptible to reduction. In practice, reduction of isoindoles (and, presumably, also isoindolenines) occurs under a variety of conditions to give isoindolines. Raney nickel has been widely used for this purpose[16, 19, 21] and generally gives high yields of the basic isoindoline, which is conveniently characterized as a salt or the methiodide. Reduction can also be effected by dissolving metal systems, typically zinc and acetic acid[15, 27, 37] or tin and hydrochloric acid.[40, 41] 1,3-Disubstituted

TABLE VIII

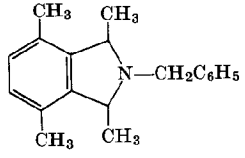
Peak Potentials and Estimated Lifetimes of Ion Radicals in Electrochemical Oxidation–Reduction of Isoindoles[a]

Isoindole	Peak potential (volts)		Lifetime (seconds)	
	Oxidation	Reduction	Cation radical	Anion radical
1,3-Diphenyl-2-methyl	0.69	−2.40	>20	<0.1
1,3,4,7-Tetraphenyl-2-methyl	0.72	−2.45	>20	2
1,3-Di-*p*-methoxyphenyl-2-methyl-4,7-diphenyl	0.60	−2.54	>20	1–2
1,2,3-Triphenyl	0.76	−2.30	>20	<0.03

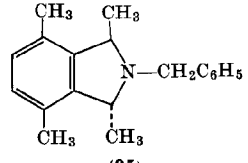
[a] Data from A. Zweig, G. Metzler, A. Maurer, and B. G. Roberts, *J. Am. Chem. Soc.* **89**, 4091 (1967).

[73] A. Zweig, G. Metzler, A. Maurer, and B. G. Roberts, *J. Am. Chem. Soc.* **89**, 4091 (1967).

isoindoles have been shown to yield predominantly the *cis*-1,3-disubstituted isoindolines by these routes. *Cis*- and *trans*-1,3,4,7-tetramethylisoindolines (**53** and **54**) have been isolated in the ratio 85:15, respectively, from the acid-catalyzed reductive dimerization of 2,5-dimethylpyrrole,[41] a reaction which probably involves 1,3,4,7-tetramethylisoindole (**51**) as an intermediate.[42] It has been found that *cis* and *trans* isomers of symmetrically 1,3-disubstituted isoindolines can be differentiated by means of the NMR spectra of their 2-benzyl derivatives.[74] The *cis* isomer (**94**), which is meso, shows a singlet for the two methylene protons of the benzyl group, while the *trans* isomer (**95**), being chiral, displays an AB pattern for the same protons in its spectrum.[75, 76] The same method has also been used to distinguish *cis* and *trans* isomers of 1,3-diphenylisoindoline.[77]

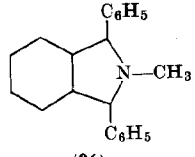


(**94**)

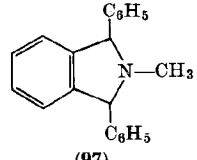


(**95**)

The perhydroisoindole system can be prepared by high-pressure hydrogenation of the isoindole over nickel on alumina at elevated temperatures.[29] The use of Raney nickel with dioxane in the reduction of 1,3-diphenyl-2-methylisoindole (**47**) gives the perhydro product (**96**), accompanied by the isoindoline (**97**).[30] An alternative route to partially hydrogenated isoindoles has been described in Section III, D.



(**96**)

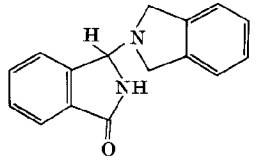


(**97**)

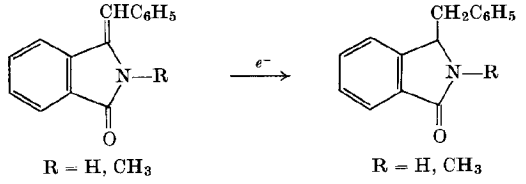
Electrolytic reduction of phthalimide and of phthalimidines which are at an oxidation level above that of isoindole, proceeds through the isoindole to the isoindoline stage, which is then stable to further

[74] C. O. Bender and R. Bonnett, *J. Chem. Soc.* p. 2186 (1968).
[75] W. F. Reynolds and T. Schaefer, *Can. J. Chem.* **42**, 2119 (1964).
[76] R. K. Hill and T. K. Chan, *Tetrahedron* **21**, 2015 (1965).
[77] L. A. Carpino, *Chem. Commun.* p. 494 (1966).

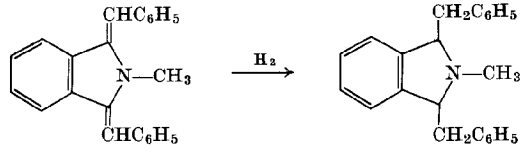
reduction. Phthalimide itself affords isoindoline in 70–80% yield, although reduction of concentrated solutions of the reagent lead to the partially reduced, dimeric substance (**98**).[78] Electrolytic reduction of benzalphthalimidines (e.g., **99**) gives the corresponding 1-benzylisoindolines.[79] Catalytic reduction of the bisbenzalisoindoline (**100**) gives the dibenzylisoindoline (**101**).[80]



(**98**)



R = H, CH_3 (**99**) R = H, CH_3 (**100**)



(**101**) (**102**)

Isoindoles are reactive toward oxidizing agents, and precautions usually advocated in the preparation of these compounds to prevent their oxidation merit careful consideration. The end products of oxidation are most often colored, resinous materials of indeterminate structure. The oxidative reactions appear to be accelerated by light and occur much more rapidly in solution than in the solid state. In a separate but possibly related process, certain isoindoles undergo polymerization in the solid state to give resins which, according to

[78] A. Dunet, J. Rollet, and A. Willemart, *Bull. Soc. Chim. France* p. 877 (1950).
[79] S. Sugasawa, *Yakugaku Zasshi* **63**, 98 (1943); *Chem. Abstr.* **44**, 7310 (1950).
[80] K. Heidenbluth, H. Toenjes, and R. Scheffler, *J. Prakt. Chem.* **30**, 204 (1965).

elemental analysis, contain no oxygen.[37] Both oxidation and polymerization are evidently related to the ease of tautomerization to the isoindolenine, since those isoindoles having a substituent on nitrogen or which are stabilized by 1,3-diaryl substitution are notably more resistant to both of these processes. The mechanistic details, however, remain to be elucidated.

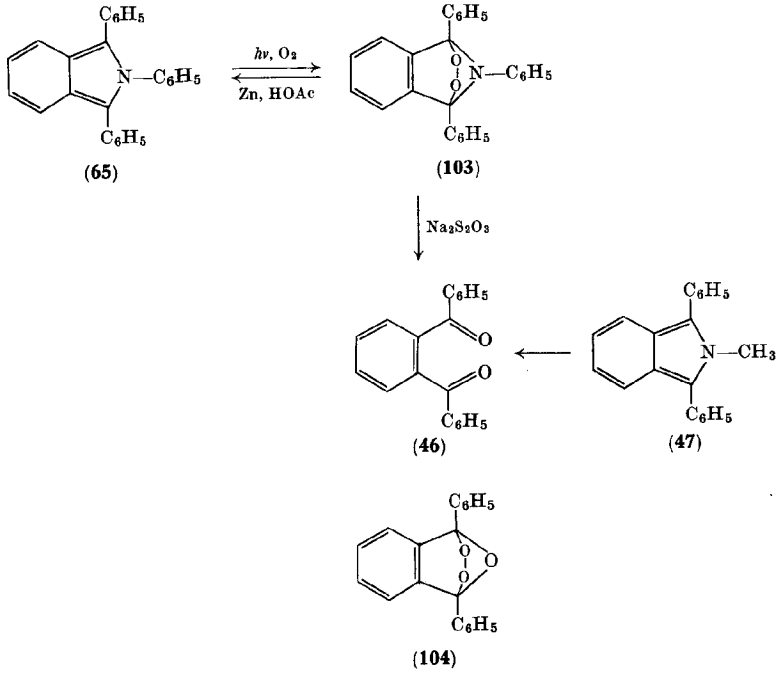
Note Added in Proof: In their study of the autoxidation of 2-butylisoindoline, Kochi and Singleton[80a] showed that 2-butylisoindole is formed and is converted by further oxidation to 2-butylphthalimide and 2-butylphthalimidine. The rate of oxidation of 2-butylisoindoline to the isoindole was found to be markedly dependent on hydrogen donor ability of the solvent and was shown to involve a free radical chain process. Autoxidation of 2-butylisoindole also appears to be a radical process since it can initiate autoxidation of 2-butylisoindoline.

A study of the electrochemical oxidation and reduction of certain isoindoles (and isobenzofurans) has been made, using cyclic voltammetry.[73] The reduction wave was found to be twice the height of the oxidation wave, and conventional polarography confirmed that reduction involved a two-electron transfer. Peak potential measurements and electrochemiluminescence intensities (see Section IV,E) are consistent with cation radicals as intermediates. The relatively long lifetime of these intermediates is attributed to steric shielding by the phenyl groups rather than electron delocalization (Table VIII).

Mercury-sensitized irradiation of 1,2,3-triphenylisoindole (**65**) in the presence of oxygen gives a peroxide (**103**).[31] This peroxide is relatively stable compared with the peroxide (**104**) derived from similar oxidation of 1,3-diphenylisobenzofuran[81] and can be reconverted to the isoindole (**65**) by pyrolysis or by treatment with zinc and acetic acid. Reduction of **103** under mild conditions affords *o*-dibenzoylbenzene (**46**) and aniline. Aerial oxidation of **47** gives **46** and methylamine, presumably via a peroxide intermediate similar to **103**.[30]

Photochemical oxidation of a mixture of 1,3,4,7-tetramethylisoindole (**51**) and its tautomer (**50**) has been found to give the isoindolenine hydroperoxide (**105**).[42] Conceivably, this hydroperoxide could disproportionate to give a hydroxyisoindolenine, since **106** is a major by-product when the condensation between 2,5-hexanedione and

[80a] J. K. Kochi and E. A. Singleton, *Tetrahedron* **24**, 4649 (1968).
[81] C. Dufraisse and S. Ecary, *Compt. Rend.* **223**, 735 (1946).



(65) (103) (46) (47) (104)

2,5-dimethylpyrrole is carried out in the presence of air. Other routes to hydroxyisoindolenines of this type have been described.[54, 55]

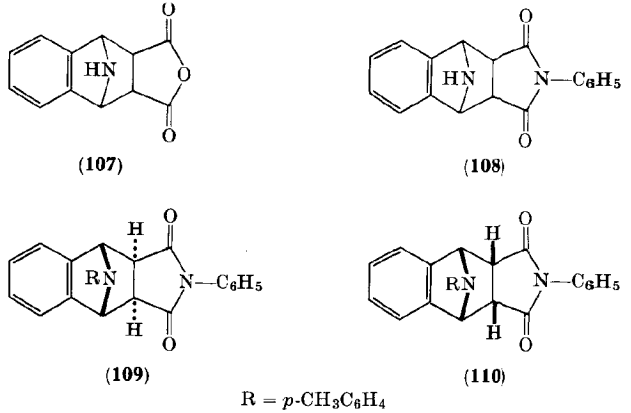
(105) (106)

Isoindoles which have a free NH group can undergo bimolecular, oxidative coupling. Thus, 1-phenylisoindole (**38**), when refluxed in benzene in the presence of air, gives a 45% yield of the dehydrobisisoindolenine (**39**),[65] a product identical with that obtained by catalytic hydrogenation of *o*-cyanobenzophenone (**37**).[34]

D. Diels–Alder Addition

The *o*-quinonoid system incorporated within the isoindole nucleus would be expected to be reactive toward dienophiles, and several isoindoles have been found to give Diels–Alder addition products. The products derived from addition to isoindoles, however, depend to a marked degree on the nature of the dienophile and on the substituents in the isoindole component.

Isoindole itself gives normal Diels–Alder addition products, (**107** and **108**), with maleic anhydride and *N*-phenylmaleimide,[5] these derivatives constituting the main evidence for formation of the parent substance. 2-Alkyl- and 2-arylisoindoles also give normal addition products with these two dienophiles.[16, 19, 21, 23] Although only one product is generally isolated, it seems likely, in view of the known tendency of several Diels–Alder adducts of isoindoles to dissociate to their components (see below), that both *exo* and *endo* stereoisomers might be formed in certain cases.[82] The reaction between 2-*p*-tolylisoindole and *N*-phenylmaleimide has been shown to give both *exo* (**109**) and *endo* (**110**) addition products.[24]

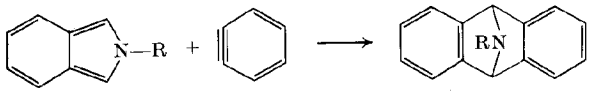


(107) (108) (109) (110)

R = *p*-$CH_3C_6H_4$

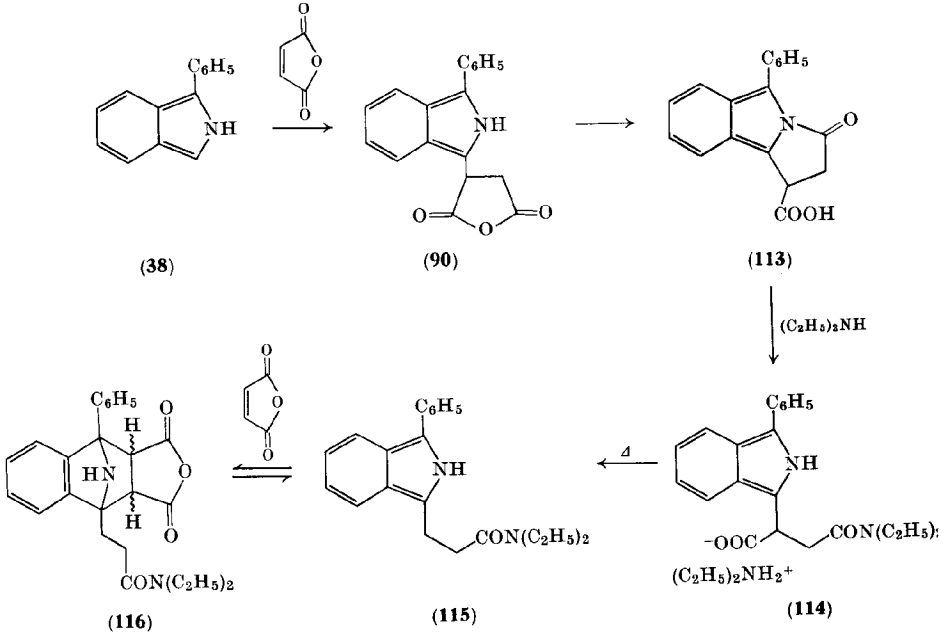
Wittig *et al.*[83] have shown that benzyne (**111**) reacts as a dienophile with 2-methyl- and 2-phenylisoindole to give bridged dihydroanthracenes (**112**, $R = CH_3, C_6H_5$).

[82] J. Sauer, *Angew. Chem. Intern. Ed. English* **6**, 16 (1967).
[83] G. Wittig, E. Knauss, and K. Niethammer, *Ann. Chem.* **630**, 10 (1960).



(111) (112)

1-Phenylisoindole (**38**), on treatment with maleic anhydride, gives a product (**90**) derived by additive substitution.[15] The analogy in this case with pyrrole chemistry[84] has been discussed above (see Section IV, B). The anhydride (**90**) undergoes a facile rearrangement in solution to yield the lactam (**113**); the latter upon treatment with diethylamine affords the propionamide derivative (**114**). Decarboxylation of **114** gives **115**, which reacts reversibly with maleic anhydride to give the normal addition product (**116**). 1-Benzyl-2-methylisoindole is reported to give both a 1:1 and a 1:2 adduct with maleic anhydride, the structures of which remain to be elucidated.[19] 1-Phenylisoindole and 1,4-naphthoquinone afford a dark blue 1:1 adduct, whose structure is also undetermined.[15]

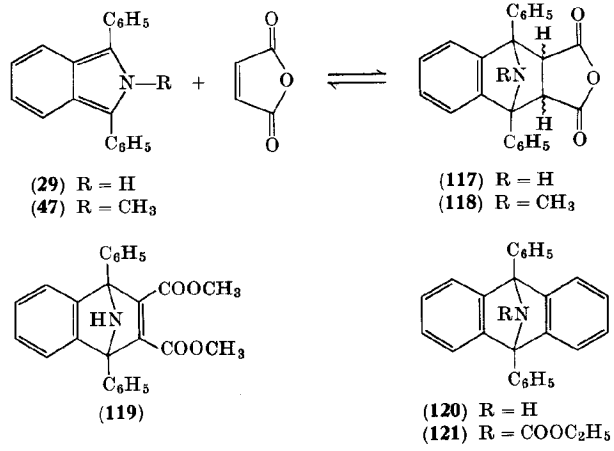


(38) (90) (113)

(116) (115) (114)

[84] O. Diels and K. Alder, *Ann. Chem.* **486**, 211 (1931).

In the case of 1,3-diphenylisoindole (**29**), Diels–Alder addition with maleic anhydride is readily reversible, and the position of equilibrium is found to be markedly dependent on the solvent. In ether, for example, the expected adduct (**117**) is formed in 72% yield, whereas in acetonitrile solution the adduct is almost completely dissociated to its components.[37] Similarly, the addition product (**118**) of maleic anhydride and 1,3-diphenyl-2-methylisoindole is found to be completely dissociated on warming in methanol.[30] The Diels–Alder products (**119** and **120**) formed by the addition of dimethyl acetylenedicarboxylate and benzyne respectively to 1,3-diphenylisoindole, show no tendency to revert to starting materials.[37] An attempt to extrude carbethoxynitrene by thermal and photochemical methods from (**121**), prepared from the adduct (**120**) by treatment with butyllithium followed by ethyl chloroformate, was unsuccessful.



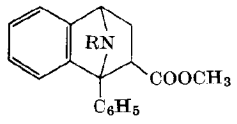
(**29**) R = H
(**47**) R = CH_3

(**117**) R = H
(**118**) R = CH_3

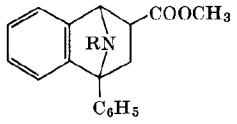
(**119**)

(**120**) R = H
(**121**) R = $COOC_2H_5$

1-Phenyl-2-methylisoindole (**88**) is reported to react with maleic anhydride in methanol to give a product derived from normal addition, followed by methanolysis and decarboxylation.[29] The alternative formulations (**122** or **123**, R = CH_3) proposed for this product are based on evidence which is less than conclusive. The corresponding 1-alkylisoindoles do not give this reaction. 1,2,3-Triphenylisoindole (**65**) is reported to be unreactive toward maleic anhydride[31]; thus, isoindole derivatives span the entire range of reactivity with this particular dienophile.

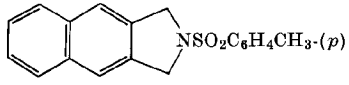


(122)

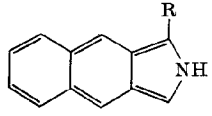


(123)

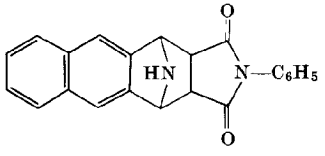
Benz[*f*]isoindole (**125**), recently prepared from the *p*-toluenesulfonyl derivative (**124**), proved to be too unstable for isolation, but could be trapped in solution as the Diels–Alder adduct (**127**).[85] The corresponding 1-phenyl derivative (**126**) was also prepared and, according to spectral measurements, reacts with maleic anhydride to give the product (**128**) derived by additive substitution. This subsequently rearranged to the adduct (**129**). The same behavior is observed in the reaction of (**126**) with *N*-phenylmaleimide. This provides the first clear indication that substitution products from isoindole derivatives and dienophiles can be converted into the "normal" addition products.



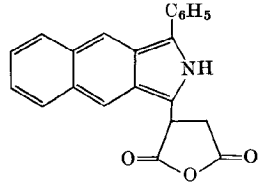
(124)



(125) R = H
(126) R = C_6H_5



(127)



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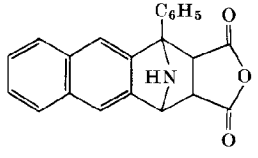

(129)

[85] J. E. Shields and J. Bornstein, *Chem. Ind. (London)* p. 1404 (1967).

E. Spectroscopic Properties

The most convenient and sensitive method for detecting the presence of an isoindole is by means of ultraviolet spectroscopy. The isoindole chromophore shows a characteristic series of bands in the range 220–390 mμ, with the band at longest wavelength usually well separated from the remainder of the spectrum and of high intensity

TABLE IX

Ultraviolet Spectra of Aryl-Substituted Isoindoles

Isoindole	Solvent	λ_{max} (log ϵ)	Ref.
1-Phenyl	Ethyl alcohol	272 (3.86), 282 (3.92), 314[a] (3.87), 325 (3.99), 357 (4.10)	37
1-*p*-Methoxyphenyl	Ethyl alcohol	272 (4.10), 282 (4.25), 309 (3.93), 358 (4.00)	35
2-*p*-Tolyl	Methyl alcohol	242 (4.50), 288 (3.94), 298 (3.94), 337 (3.62)	24
2-*p*-Anisyl	Methyl alcohol	245 (4.45), 287 (4.02), 298 (4.03), 337 (3.66)	24
1,3-Diphenyl	Ethyl alcohol	228[a] (4.24), 237 (4.27), 268[a] (4.22), 273 (4.27), 322 (4.13), 335 (4.16), 387 (4.37)	27, 37
1,3-Diphenyl-2-methyl	Ethyl alcohol	228 (4.47), 268[a] (4.13), 276 (4.20), 332 (4.01), 371 (4.27)	27, 37
1,3-Diphenyl-2-methyl	Dioxane	268 (3.98), 276 (4.12), 333 (4.00), 375 (4.28)	31
1,2,3-Triphenyl	Not indicated	235 (4.50), 270[a] (4.19), 277 (4.26), 314 (3.98), 328 (4.02), 374 (4.23)	56
1,2,3-Triphenyl	Dioxane	278 (4.23), 326 (4.00), 376 (4.21)	31

[a] Shoulder or inflexion.

($\epsilon \sim 10{,}000$). The position of this band (and, to a lesser extent, its intensity) is noticeably dependent on the substitution pattern on the isoindole nucleus. For example, 1-arylisoindoles have their longest wavelength absorption in the range 355–360 mμ, whereas 2-arylisoindoles have the same band at 335–340 mμ with lower extinction coefficients. From the limited examples available, a hypsochromic

shift of the long wavelength band would appear to be the rule in going from isoindoles unsubstituted on nitrogen to the corresponding *N*-substituted derivatives. This applies even when the *N*-substituent is an aryl grouping. Ultraviolet spectral data for several isoindoles are given in Table IX.

Accurate, quantitative spectroscopic data for the simple alkyl-substituted derivatives of isoindole are not available, either because of their inherent instability or tendency to tautomerize to isoindolenines. However, the presence of an isoindole in a tautomeric mixture can be readily discerned by means of ultraviolet spectroscopy.[42]

TABLE X

ELECTROCHEMILUMINESCENCE AND FLUORESCENCE EMISSION FROM ISOINDOLES[a]

Isoindole	λ_{max} (ecl. or fluor.) mμ	Quantum yield (fluor.)	Relative ecl. intensity
1,3-Diphenyl-2-methyl	453	0.73	—
1,3,4,7-Tetraphenyl-2-methyl	490	0.53	3.8
1,3-*p*-Anisyl-4,7-diphenyl-2-methyl	507	0.52	7.2
1,2,3-Triphenyl	448	0.11	—

[a] Data of A. Zweig, G. Metzler, A. Maurer, and B. G. Roberts, *J. Am. Chem. Soc.* **89**, 4091 (1967). Electrochemiluminescence, ecl.; fluorescence, fluor.

Emission spectra have been recorded for four aryl-substituted isoindoles under conditions of electrochemical stimulation.[73] Electrochemiluminescence, which was easily visible in daylight, was measured at a concentration of 2–10 m*M* of emitter in *N*,*N*-dimethylformamide with platinum electrodes. Emission spectra due to electrochemiluminescence and to fluorescence were found to be identical, and quantum yields for fluorescence were obtained by irradiation with a calibrated light source. Values are given in Table X. As with peak potentials determined by cyclic voltammetry, the results of luminescence studies are interpreted in terms of radical ion intermediates.[73]

The infrared spectra of a number of isoindoles have been reported. All apparently show an intense band at 1600 cm^{-1}, and in isoindoles where nitrogen is unsubstituted, the NH stretching absorption occurs as a strong, sharp band at about 3450 cm^{-1}.[35,37,39,42] Very little information is available concerning the nuclear magnetic

resonance spectra of isoindoles, although this method could provide a useful indication of whether the isoindole system can support an induced diamagnetic ring current, as would be predicted on the basis of the aromaticity of isoindoles.

Pyridopyrimidines:

1,3,5-, 1,3,6-, 1,3,7-, and 1,3,8-Triazanaphthalenes

W. J. IRWIN and D. G. WIBBERLEY

Department of Pharmacy, University of Aston in Birmingham, Birmingham, England

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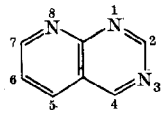
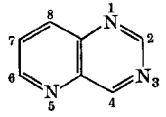
I. Introduction

The pyridopyrimidines discussed in this review are derived by the ortho fusion of the pyridine and pyrimidine rings through ring carbon atoms. There are four such compounds for which the nomenclature and numbering of *Chemical Abstracts* (**1**–**4**) will be used. Alternative names used in the literature are 1,3,8-triazanaphthalene (**1**), 1,3,5-triazanaphthalene (**2**), 1,3,7-triazanaphthalene or copazoline (**3**), and 1,3,6-triazanaphthalene (**4**). There has been no previous review of the



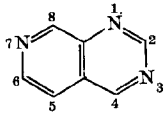
(1)

Pyrido[2,3-*d*]pyrimidine



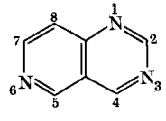
(2)

Pyrido[3,2-*d*]pyrimidine



(3)

Pyrido[3,4-*d*]pyrimidine

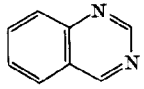


(4)

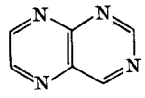
Pyrido[4,3-*d*]pyrimidine

chemistry of these ring systems, but the covalent hydration [1, 2] and nucleophilic substitution reactions [3] of pyridopyrimidines are discussed in earlier volumes of this series.

The present review covers the literature to the end of 1967 and all original sources have been consulted. Syntheses of each of the four ring systems are summarized separately, but physical, chemical, and biological properties are considered generally. Many pyridopyrimidines were initially synthesized for a study of biological activity or physical properties because of the close structural relationship of these systems to the quinazolines (**5**) and pteridines (**6**). Recent reviews [4, 5, 6] have discussed these related compounds.



(5)



(6)

II. Syntheses

A. Pyrido[2,3-*d*]pyrimidines

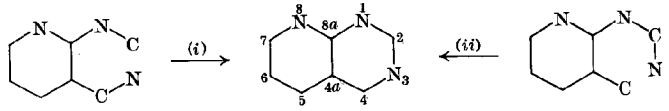
Due in the main to the prolific work of G. H. Hitchings and his co-

[1] A. Albert and W. L. F. Armarego, *Advan. Heterocyclic Chem.* **4**, 1–42 (1964).
[2] D. D. Perrin, *Advan. Heterocyclic Chem.* **4**, 43–74 (1964).
[3] R. G. Shepherd and J. L. Fedrick, *Advan. Heterocyclic Chem.* **4**, 146–423 (1964).
[4] W. L. F. Armarego, *Advan. Heterocyclic Chem.* **1**, 253–309 (1963).
[5] W. Pfleiderer, *Angew. Chem. Intern. Ed. English* **3**, 114 (1964).
[6] R. C. Elderfield and A. C. Mehta, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 9, p. 1. Wiley, New York, 1967.

workers many more aromatic pyrido[2,3-*d*]pyrimidines are known than all of the derivatives of the three other systems. A wide variety of synthetic routes, from both pyridines and pyrimidines, have been investigated.

1. *From Pyridines*

The final step in the syntheses of pyrido[2,3-*d*]pyrimidines from pyridines has involved the formation of the bonds 1–8*a*, 1–2, and 4–4*a*, but the most useful methods are those which form the 2–3 (*i*) and 3–4 (*ii*) bonds.



The mechanism of the reactions, and hence the detailed nature of the intermediates involved, are often uncertain. The syntheses which follow are, therefore, subdivided according to the starting material and not the mode of cyclization.

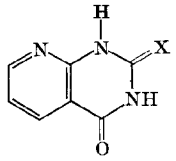
a. *From 2-Aminonicotinic Acids.* Extensions of the von Niementowski quinazolone synthesis [4, 7] have proved a fruitful source of pyrido[2,3-*d*]pyrimidin-4(3*H*)-ones. This method was used by Klisiecki and Sucharda [8] in the first claimed synthesis of a pyrido[2,3-*d*]pyrimidine, when it was suggested that the reaction of 2-aminonicotinic acid (**7**) with formamide yielded pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**8**).

(7) (8)

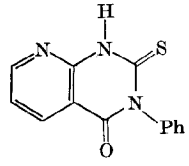
Difficulty was experienced when repetition of this preparation was attempted, [9] but conditions were soon found that enabled the pyridopyrimidine to be obtained in good yield. This product, however,

[7] T. A. Williamson, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 5, p. 324. Wiley, New York, 1957.
[8] L. Klisiecki and E. Sucharda, *Roczniki Chem.* **3**, 251 (1923).
[9] R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.* **77**, 2256 (1955).

melted considerably lower[9-11] than that reported previously.[8] Similar reactions of 2-aminonicotinic acid with urea,[9,10] thiourea,[9,10] and phenylthiourea[12] yielded the 2,4-dione (**9**, X = O), the 2-thione analog (**9**, X = S), and 3-phenyl-2-thioxopyrido[2,3-*d*]pyrimidin-4(1*H*, 3*H*)-one (**10**).



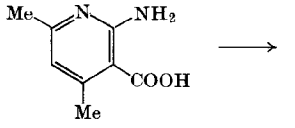
(**9**)



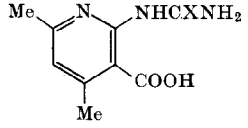
(**10**)

The use of substituted 2-aminonicotinic acids[11,13] has enabled a series of pyrido[2,3-*d*]pyrimidines, which have 5-, 6-, and 7-alkyl and aryl substituents, to be obtained.

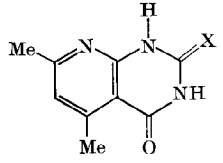
Undoubtedly these reactions proceed via an intermediate ureido or thioureido derivative. These compounds have been obtained by Dornow and Hahmann[14] by the action of potassium cyanate or ammonium isothiocyanate on 2-amino-4,6-dimethylnicotinic acid (**11**), but whereas the urea (**12**, X = O) was converted into the pyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (**13**, X = O) by the action of heat, the thiourea (**12**, X = S) was unchanged after similar treatment.



(**11**)



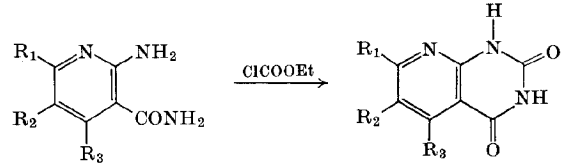
(**12**)



(**13**)

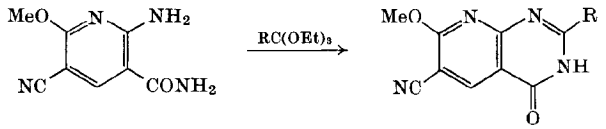
[10] V. Oakes, R. Pascoe, and H. N. Rydon, *J. Chem. Soc.* p. 1045 (1956).
[11] Wellcome Foundation, British Patent No. 774, 094 and 774,095 (1957); *Chem. Abstr.* **52**, 2097 (1958).
[12] A. P. Bhaduri and N. M. Khanna, *Indian J. Chem.* **4**, 447 (1966).
[13] G. H. Hitchings and R. K. Robins, U.S. Patent No. 2,697,710 (1954); *Chem. Abstr.* **50**, 1093 (1956).
[14] A. Dornow and O. Hahmann, *Arch. Pharm.* **290**, 61 (1957).

b. *From 2-Aminonicotinamides.* 2-Aminonicotinamides (**14**) have been shown to react readily with ethyl chloroformate to yield pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (**15**).[14,15] Although these compounds may be synthesized from 2-aminonicotinic acids and urea, as described previously, process **14** → **15** is advantageous in that less drastic conditions are necessary.

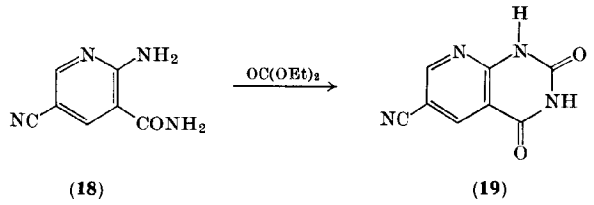


(**14**) (**15**)

This approach has been extended by Tieckelmann, Mulvey, and Cottis[16,17] to 2-amino-5-cyanonicotinamides (**16** and **18**), which were prepared directly by partial hydrolysis of the corresponding dinitriles. Diethyl carbonate, ethyl orthoacetate, and ethyl orthoformate[15,16] all underwent reaction to yield the corresponding pyrido[2,3-*d*]pyrimidines (**17** and **19**).



(**16**) (**17**)

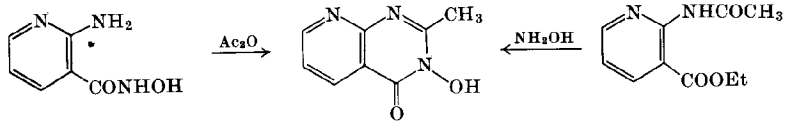


(**18**) (**19**)

[15] A. Dornow and D. Wille, *Chem. Ber.* **98**, 1505 (1965).
[16] D. M. Mulvey, S. G. Cottis, and H. Tieckelmann, *J. Org. Chem.* **29**, 2903 (1964).
[17] D. M. Mulvey, *Dissertation Abstr.* **26**, 5043 (1966).

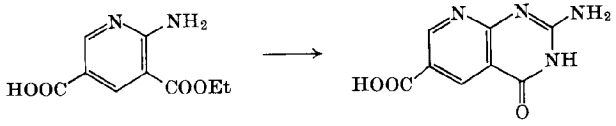
Acid chlorides,[18] acetic anhydride,[15] and formamide[19, 20] have also been used to synthesize pyrido[2,3-*d*]pyrimidines from 2-amino-nicotinamides, although in the last case high temperatures were necessary. It is suspected that all the foregoing cyclizations proceed via initial acylation of the 2-amino group to yield an intermediate 2-amidonicotinamide.

Only one cyclic hydroxamic acid which contains the pyrido[2,3-*d*]-pyrimidine ring system has been reported.[21] This is 2-methyl-3-hydroxypyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**21**) which was prepared by the action of acetic anhydride on 2-aminonicotinhydroxamic acid (**20**) or from ethyl 2-acetamidonicotinate (**22**) and hydroxylamine. In view of the known antibacterial activity of certain cyclic hydroxamic acids[22] further work on these compounds would be of interest.



(**20**) (**21**) (**22**)

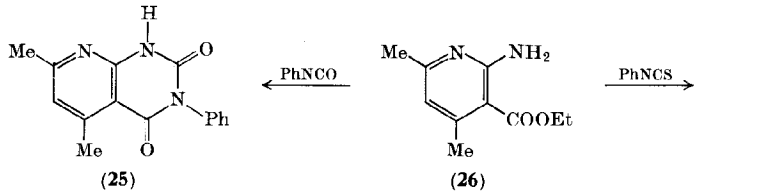
c. *From Ethyl 2-Aminonicotinates.* The reaction of guanidine with 6-amino-5-ethoxycarbonylnicotinic acid (**23**) yields 2-aminopyrido-[2,3-*d*]pyrimidin-4(3*H*)-one-6-carboxylic acid (**24**).[16]



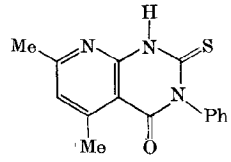
(**23**) (**24**)

Amino esters (**26**) have also been shown[15] to yield pyrido[2,3-*d*]-pyrimidin-4(3*H*)-ones (**25**, **27**) when treated with isocyanates and isothiocyanates. The reactions proceed via intermediate ureido and thioureido derivatives.

[18] Rhone-Pouleux, S. A., Netherlands Patent No. 6,507,580 (1965); *Chem. Abstr.* **64**, 12698 (1966).
[19] S. G. Cottis and H. Tieckelmann, *J. Org. Chem.* **26**, 79 (1961).
[20] S. G. Cottis, Ph.D. Thesis, University of Buffalo, Buffalo, New York, 1962.
[21] D. Harrison and A. C. B. Smith, *J. Chem. Soc.* p. 2157 (1960).
[22] R. T. Coutts, *Can. J. Pharm. Sci.* **2**, 27 (1967).

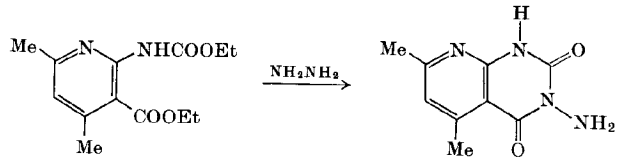


(**25**) (**26**)



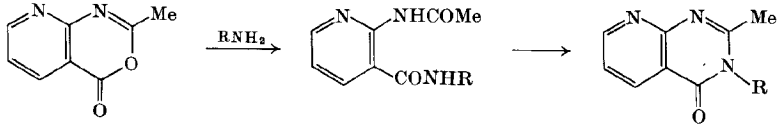
(**27**)

The carbamate (**28**) reacts with hydrazine hydrate to yield 3-amino-5,7-dimethylpyrido[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione (**29**).[15]



(**28**) (**29**)

d. *From Pyrido*[2,3-*d*]-[1,3]-*oxazin*-4-*ones.* 2-Methylpyrido[2,3-*d*]-[1,3]-oxazin-4-one (**30**), obtained by the action of acetic anhydride on 2-aminonicotinic acid, has been shown to be a useful intermediate in the synthesis of pyrido[2,3-*d*]pyrimidin-4(3*H*)-ones.[12] Treatment of the pyridooxazine (**30**) with various primary amines yielded a series of 3-substituted 2-methylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones (**32**). As in similar preparations of quinazolones[7] and pyrido[3,2-*d*]pyrimidones[23] from fused oxazin-4-ones, this reaction undoubtedly proceeds via cyclization of the amide (**31**).

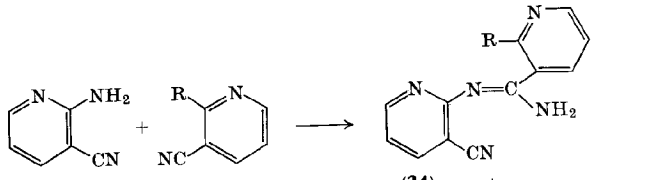


(**30**) (**31**) (**32**)

[23] W. J. Irwin and D. G. Wibberley, *J. Chem. Soc.* p. 4240 (1965).

Pyrido[2,3-*d*]-[1,3]-oxazin-4-ones were first prepared by Dornow *et al.*,[14,15] but were not converted into pyridopyrimidines by these workers.

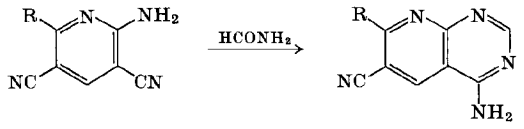
e. *From 2-Aminonicotinonitrile.* Amination of 2-chloronicotinonitrile yielded, in addition to the expected 2-aminonicotinonitrile (**33**), a small amount of a high-melting yellow product.[24] This was subsequently shown to be 2-[3-(2-aminopyridyl)]-4-aminopyrido[2,3-*d*]-pyrimidine (**35**, R = NH_2) which was produced by the dimerization of 2-aminonicotinonitrile.[25] The reaction has been extended to the preparation of 4-amino-2-(3-pyridyl)pyrido[2,3-*d*]pyrimidine (**35**, R = H) from 2-aminonicotinonitrile and nicotinonitrile,[26] and has also proved useful in the synthesis of other fused 4-aminopyrimidines.[26-28]



(33) (34) (35)

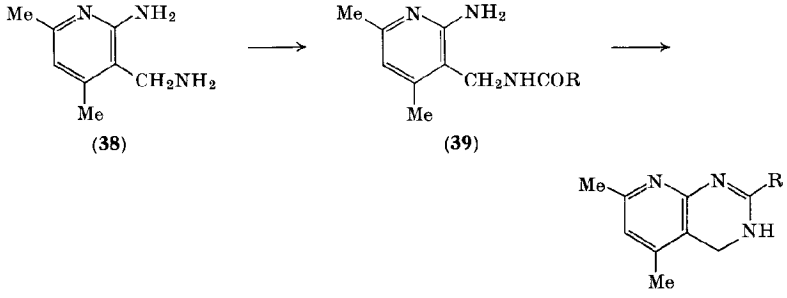
This reaction is believed to proceed via an amidine (**34**) and it has been shown[26] that the reactivity of the nitrile group toward nucleophiles is a more important factor than amine basicity in controlling cyclization.

[24] E. C. Taylor and A. J. Crovetti, *J. Org. Chem.* **19**, 1633 (1954).
[25] E. C. Taylor, A. J. Crovetti, and R. J. Knopf, *J. Am. Chem. Soc.* **80**, 427 (1958).
[26] E. C. Taylor and A. L. Borror, *J. Org. Chem.* **26**, 496 (1961).
[27] E. C. Taylor and M. W. Kalenda, *J. Amer. Chem. Soc.* **78**, 5108 (1956).
[28] E. C. Taylor, R. J. Knopf, and A. L. Borror, *J. Am. Chem. Soc.* **82**, 3152 (1960).



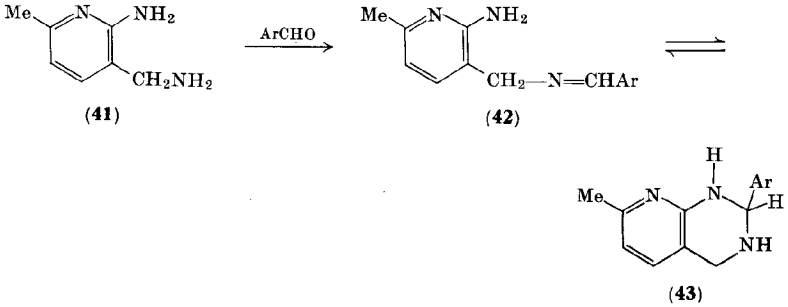
(36) (37)

Good yields of pyrido[2,3-*d*]pyrimidines (**37**) were also obtained by the action of formamide on *o*-amino nitriles (**36**).[16] Reduction of 2-amino-4,6-dimethylnicotinitrile yields the 3-aminomethyl compound (**38**). Acylation to the 3-acylaminomethyl derivative (**39**), followed by cyclization, by means of heat or phosphoryl chloride, yielded the dihydropyrido[2,3-*d*]pyrimidines (**40**).[29]



(38) (39) (40)

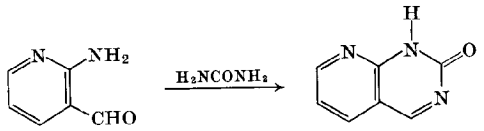
Tetrahydropyrido[2,3-*d*]pyrimidines (**43**) have been obtained via the anils (**42**) prepared from similar 2-amino-3-aminomethylpyridines (**41**) and aromatic aldehydes.[30]



(41) (42) (43)

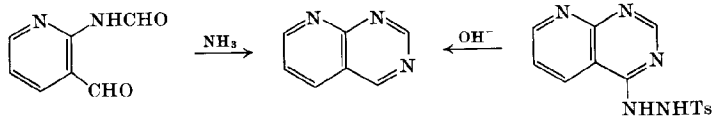
[29] P. J. Vanderhorst and C. S. Hamilton, *J. Am. Chem. Soc.* **75**, 656 (1953).
[30] H. Suter, E. Habicht, and H. Martin, Swiss Patent No. 331,989 (1958); *Chem. Abstr.* **53**, 5292 (1959).

f. *From 2-Aminonicotinaldehyde.* Fusion of 2-aminonicotinaldehyde (**44**) with urea yielded pyrido[2,3-*d*]pyrimidin-2(1*H*)-one (**45**).[31] Similar treatment of the aldehyde with formamide gave no isolable product.[10]



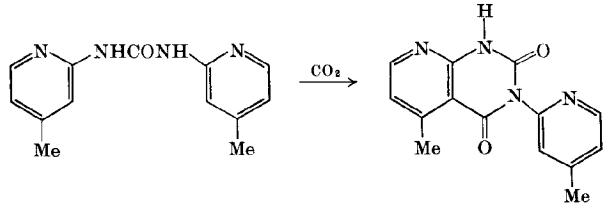
(**44**) (**45**)

Formylation of the amino aldehyde, and subsequent treatment of the amide (**46**) with ammonia enabled Armarego[32,33] to prepare pyrido[2,3-*d*]pyrimidine (**1**). This compound was also obtained by the decomposition of the tosylhydrazino compound (**47**).[32,33]



(**46**) (**1**) (**47**)

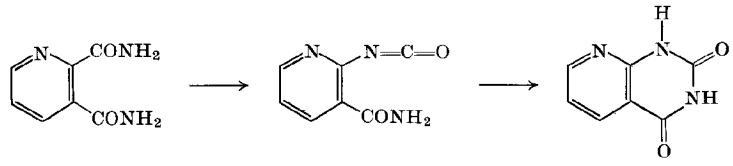
g. *From 2-Aminopyridines.* A novel route to pyrido[2,3-*d*]pyrimidines is the reaction of 2-amino-4-picoline with carbon dioxide.[34] The reactants are heated together at 250°, under pressures of 8500 atm, for several hours, to yield the pyrido[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione (**49**) through the intermediate formation of the symmetrical urea (**48**).



(**48**) (**49**)

[31] A. Albert and F. Reich, *J. Chem. Soc.* p. 1370 (1960).
[32] W. L. F. Armarego, *Proc. Chem. Soc.* p. 450 (1961).
[33] W. L. F. Armarego, *J. Chem. Soc.* p. 4094 (1962).
[34] W. W. Gilbert, U.S. Patent No. 2,680,741 (1954); *Chem. Abstr.* **49**, 6322 (1955).

h. *From Pyrido-2,3-dicarboxyamide.* An interesting synthesis of pyrido[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione (**51**) is afforded by the reaction of quinolinamide (**50**) with hypobromite.[35] The reaction is noteworthy in that only the pyrido[2,3-*d*]pyrimidine isomer was isolated although it is conceivable that pyrido[3,2-*d*]pyrimidine-2,-4(1*H*,3*H*)-dione might be produced simulaneously.

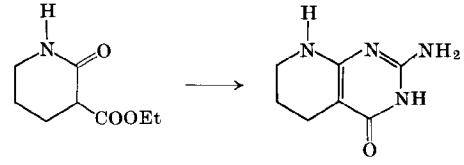


(**50**) (**51**)

6-Methylpyrido[2,3-*d*]pyrimidin-2,4(1*H*,3*H*)-dione has also been prepared by this method,[36] which has also been used for the synthesis of other bicyclic systems.[37]

i. *From Nicotinic Acid.* Amidation of nicotinic acid yielded 2-(3-pyridyl)pyrido[2,3-*d*]pyrimidine in addition to the expected nicotinamide.[38]

j. *From Piperidines.* The reaction of 3-ethoxycarbonylpiperidine-2-one (**52**) with guanidine gave 2-amino-5,6,7,8-tetrahydropyrido-[2,3-*d*]pyrimidin-4(3*H*)-one (**53**).[39]



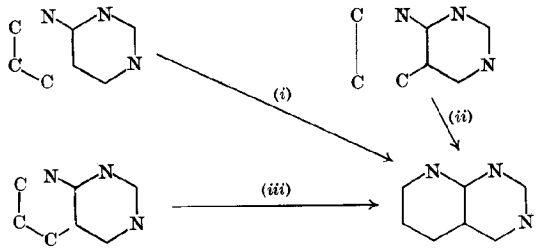
(**52**) (**53**)

This is the first synthesis of pyrido[2,3-*d*]pyrimidines in which both nitrogen atoms of the pyrimidine ring have been supplied by the reagent. In view of the success of similar syntheses of pyrido[4,3-*d*]-pyrimidines this route would appear to be capable of wide extension.

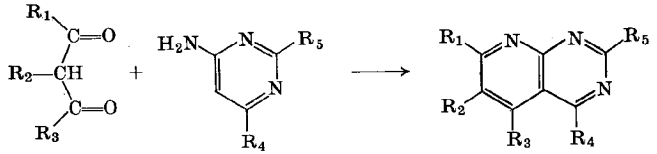
[35] A. C. Mclean and F. S. Spring, *J. Chem. Soc.* p. 2582 (1949).
[36] V. Oakes and H. N. Rydon, *J. Chem. Soc.* p. 4433 (1956).
[37] R. G. Jones, *J. Org. Chem.* **25**, 956 (1960).
[38] J. Bayer, *Acta Chim. Acad. Sci. Hung.* **48**, 353 (1966).
[39] J. DeGraw and L. Goodman, *Can. J. Chem.* **41**, 3137 (1963).

2. *From Pyrimidines*

Three general approaches to the synthesis of pyrido[2,3-*d*]pyrimidines from pyrimidines are available, all of which utilize an appropriately substituted 4-aminopyrimidine. The pyridine ring may be formed by the addition of three (route *i*), or two (route *ii*) carbon atoms, or by the intramolecular cyclization of a propionyl derivative (route *iii*).



a. *Route (i) Syntheses.* The major synthetic route to pyrido[2,3-*d*]-pyrimidines bearing amino, oxo, or thioxo substituents in the pyrimidine ring (**56**) is the reaction of 4-aminopyrimidines (**55**) with 1,3-dicarbonyl compounds (**54**). The reactions are frequently carried out in the presence of phosphoric acid, sulfuric acid, or phosphorus pentoxide, and the pyrido[2,3-*d*]pyrimidine is usually obtained directly from the reaction mixture.



(**54**) (**55**) (**56**)

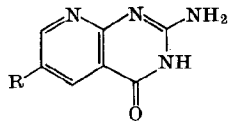
The reaction involves an electrophilic attack into the 5-position of the pyrimidine ring and thus only those pyrimidines that are activated toward electrophilic substitution [40] by the presence of electron-donating substituents at the 2- and 4-positions undergo cyclization. 2,4,6-Triaminopyrimidine, 6-aminouracil, 6-amino-2-thiouracil, 4-amino-2,4 dimercaptopyrimidine, 2,4-diaminopyrimidin-6(1*H*)-one, and various 4-amino-*N*-alkyl and aryl pyrimidones have all been converted into pyrido[2,3-*d*]pyrimidines when treated with the required

[40] B. Lythgoe, A. R. Todd, and A. Topham, *J. Chem. Soc.* p. 316 (1944).

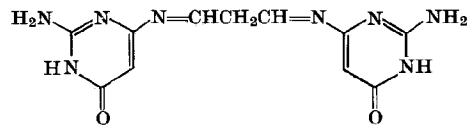
carbonyl compounds. 4-Amino-2-methylpyrimidin-6(1*H*)-one and 2,4-diamino-6-methylpyrimidine failed to react.[41]

In view of the wide variation of carbonyl compounds which may be used in this reaction, it is proposed to divide this section further on the basis of the carbonyl function involved.

i. Dialdehydes. Sodium nitromalondialdehyde and 2,4-diaminopyrimidin-6(1*H*)-one yielded 2-amino-6-nitropyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**57**, R = NO_2) when heated under reflux with aqueous alkali.[42,43] Malondialdehyde tetramethyl acetal, however, gave the dianil (**58**) initially which cyclized to yield the pyrido[2,3-*d*]pyrimidine (**57**, R = H) on treatment with sulfuric acid.[42]



(**57**)



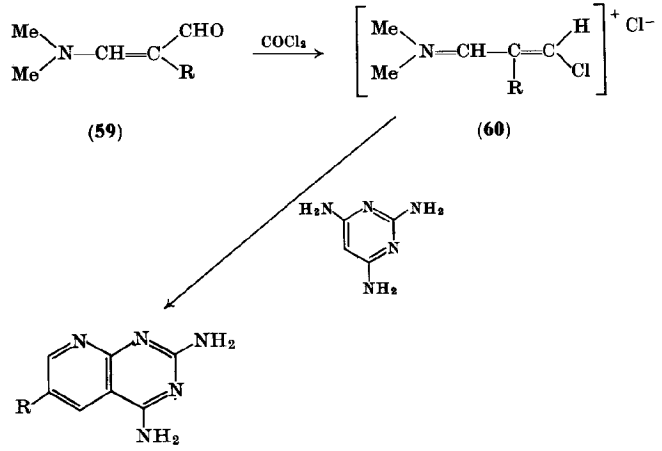
(**58**)

If the structure of the dianil is as shown (**58**) this is a rare example of initial attack taking place at the 4-amino substituent.

An interesting variation of this procedure relies upon the formation of malondialdehyde precursors *in situ*.[44–46a] Vinylogs of Vilsmeier–Haack intermediates (**60**),[47] formed from dimethylaminoacroleins (**59**) and phosgene, undergo reaction with 2,4,6-triaminopyrimidine to yield 6-alkyl- and 6-aryl-substituted 2,4-diaminopyrido[2,3-*d*]-pyrimidines (**61**). Dimethylaminoacroleins were found to be unsatisfactory.[44]

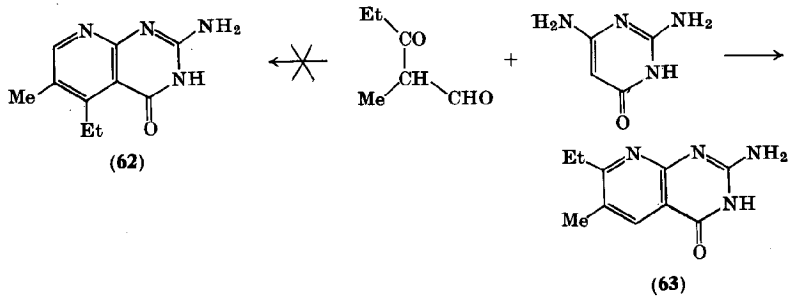
ii. Keto aldehydes. Keto aldehydes have proved useful for the synthesis of pyrido[2,3-*d*]pyrimidines which are disubstituted in the

[41] R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.* **80**, 3449 (1958).
[42] R. Bernetti, F. Mancini, and C. C. Price, *J. Org. Chem.* **27**, 2863 (1962).
[43] R. Bernetti, Ph.D. Thesis, University of Pennsylvania, Philadelphia, Pennsylvania, 1959.
[44] B. S. Hurlbert and B. F. Valenti, *J. Med. Chem.* **11**, 708 (1968).
[45] G. H. Hitchings and B. S. Hurlbert, U.S. Patent No. 3,288,792(1966); *Chem. Abstr.* **66**, 6163 (1967).
[46] Wellcome Foundation, Belgian Patent No. 620,347 (1963); *Chem. Abstr.* **59**, 7543 (1963).
[46a] Wellcome Foundation, Belgian Patent No. 657,922 (1965); *Chem. Abstr.* **64**, 15896 (1966).
[47] Z. Arnold and F. Šorm, *Chem. Listy* **51**, 1082 (1957).



(59) (60) (61)

pyridine ring. The reaction is complicated by the fact that two isomeric pyridopyrimidines may be formed. Thus, 2,4-diaminopyrimidin-6(1*H*)-one and 2-methyl-3-oxopentanal could theoretically produce either the 5-ethyl (**62**) or the 7-ethyl (**63**) isomer. In fact, 2-amino-7-ethyl-6-methylpyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**63**) is the only product isolated, and in all cases examined it has been found that only one isomer is obtained.[41, 48–50] In every instance the pyridopyrimidine

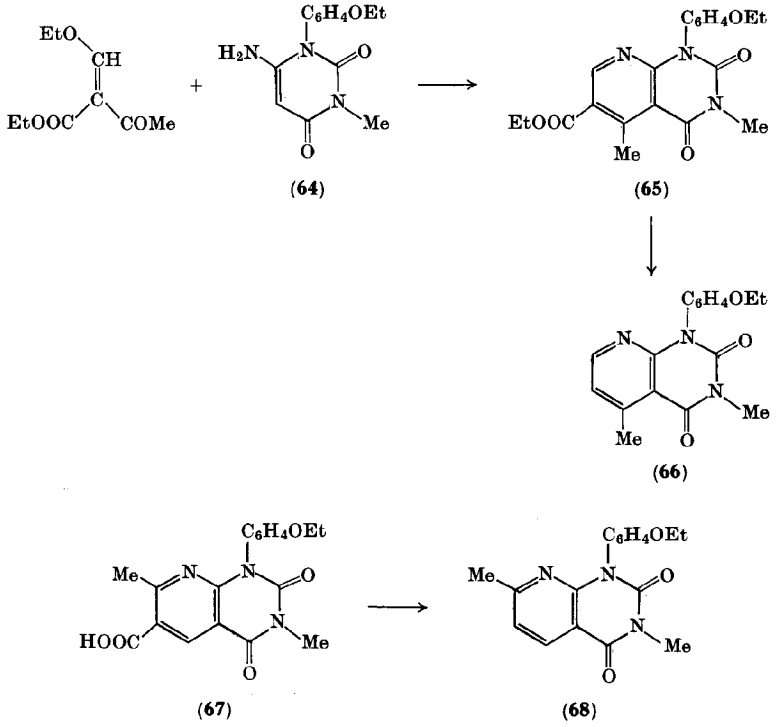


(62) (63)

[48] Wellcome Foundation, British Patent No. 774,095 (1957); *Chem. Abstr.* **52**, 2097 (1958).
[49] G. H. Hitchings and R. K. Robins, U.S. Patent No. 2,749,344 (1956); *Chem. Abstr.* **51**, 1304 (1957).
[50] G. H. Hitchings and R. K. Robins, U.S. Patent No. 3,021,332 (1962); *Chem. Abstr.* **57**, 839 (1962).

which was isolated was the one produced by reaction of the aldehyde function with the 5-position of the pyrimidine ring.

The yield of pyrido[2,3-*d*]pyrimidine has been shown to be significantly reduced when unsubstituted keto aldehydes are used.



(64) (65) (66) (67) (68)

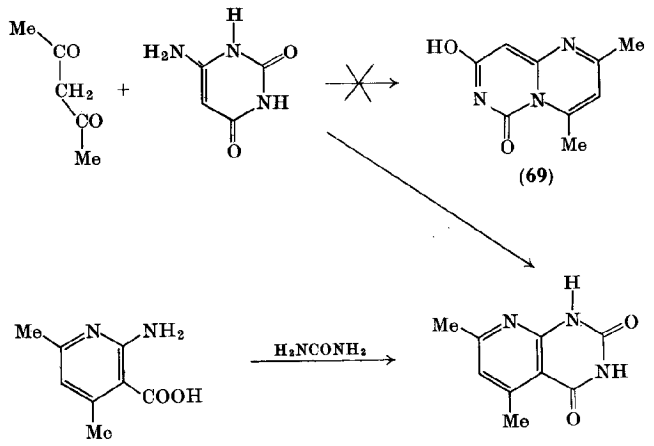
This has been attributed[41] to the self-condensation reactions of these compounds,[51, 52] e.g., acetylacetaldehyde yields *s*-triacetylbenzene.[51]

iii. Ethoxymethylene compounds. Ethoxymethyleneacetoacetates and ethoxymethyleneacetylacetones[53, 54] have been used to prepare pyrido[2,3-*d*]pyrimidines containing 6-ethoxycarbonyl or 6-acetyl

[51] L. Claisen and N. Stylos, *Ber. Deut. Chem. Ges.* **21**, 1144 (1888).
[52] L. Claisen, *Ann. Chem.* **281**, 307 (1894).
[53] M. Ridi, *Ann. Chim. (Rome)* **49**, 944 (1959).
[54] M. Ridi, *Ann. Chim. (Rome)* **50**, 405 (1960).

substituents. Thus, the substituted uracil (**64**) and ethyl ethoxymethyleneacetoacetate yielded the pyrido[2,3-*d*]pyrimidine (**65**). Hydrolysis and decarboxylation gave 3,5-dimethyl-1-(4-ethoxyphenyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**66**) which was not identical with the other possible isomer (**68**), prepared by decarboxylation of the known acid (**67**).

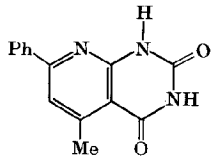
iv. Diketones. 4-Aminopyrimidines also react readily with 1,3-diketones to yield various 5-, 6-, and 7-substituted pyrido[2,3-*d*]-pyrimidines.[41, 48–50, 55] Acetyl acetone and 6-aminouracil, for example, yielded 5,7-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**70**) when heated together in phosphoric acid. The alternative pathway, to yield the pyrimido[1,2-*c*]pyrimidine (**69**), was discounted by a second synthesis from 2-amino-4,6-dimethylnicotinic acid.



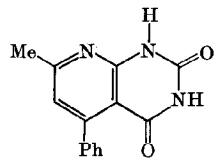
With unsymmetrical diketones the orientation of the reaction is again controlled by the reaction of the most reactive carbonyl group with the 5-position of the pyrimidine ring. Thus, benzoyl acetone and 6-aminouracil gave 5-methyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione (**71**), in preference to the 5-phenyl isomer (**72**).[41]

v. Acyl acetates. β-Keto esters have proved useful for the preparation of pyrido[2,3-*d*]pyrimidin-7(8*H*)-ones bearing alkyl and aryl

[55] M. Ridi, S. Checchi, and P. Papini, *Ann. Chim.* (*Rome*) **45**, 439 (1955).

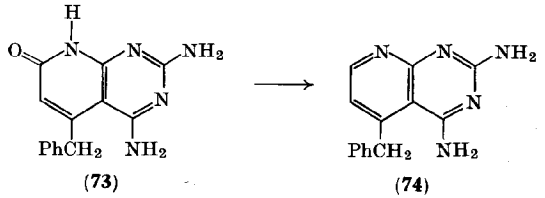


(**71**)



(**72**)

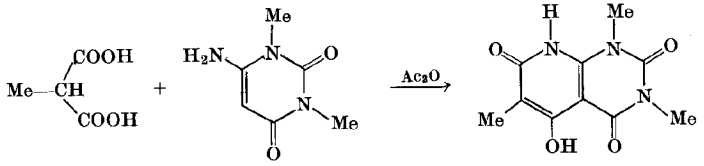
substituents in the 5- and 6-positions.[55–59] Again the reaction proceeds so that the most reactive carbonyl group (i.e., the ketone) attacks the 5-position of the pyrimidine ring. Thus, ethyl α-benzylacetoacetate and 2,4,6-triaminopyrimidine, in diphenyl ether, yield 2,4-diamino-5-benzylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**73**).[56]



Structural proof has been offered by chlorination, thionation, and reduction to yield the pyrido[2,3-*d*]pyrimidine (**74**) which has been subjected to NMR analysis.[56]

vi. Malonates. A further variation of the carbonyl reagent which is useful for 7-substituted 6-hydroxypyrido[2,3-*d*]pyrimidin-7(8*H*)-ones is the use of malonic acid derivatives.[60–62] Thus, methylmalonic acid and 4-amino-1,3-dimethyluracil, with acetic anhydride as catalyst, yielded the pyrido[2,3-*d*]pyrimidine (**75**).

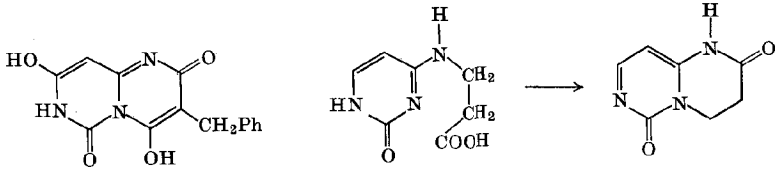
[56] B. S. Hulbert, K. W. Ledig, P. Stenbuck, B. F. Valenti, and G. H. Hitchings, *J. Med. Chem.* **11**, 703 (1968).
[57] Wellcome Foundation, British Patent No. 913,710 (1962); *Chem. Abstr.* **60**, 1771 (1964).
[58] G. H. Hitchings and K. W. Ledig, U.S. Patent No. 2,937,284 (1960); *Chem. Abstr.* **55**, 25999 (1961).
[59] Wellcome Foundation, Belgian Patent No. 658,069 (1965); *Chem. Abstr.* **64**, 5110 (1966).
[60] H. C. Scarborough, *J. Org. Chem.* **29**, 219 (1964).
[61] E. Ziegler and E. Nölken, *Monatsh. Chem.* **92**, 1184 (1961).
[62] H. C. Scarborough, U.S. Patent No. 3,139,432 (1964); *Chem. Abstr.* **61**, 7024 (1964).



(75)

The trione formulation (**75**) was supported by NMR measurements.[60]

It has been reported that 6-aminouracil and di-(2,4-dichlorophenyl)-benzylmalonate yield the pyrimido[1,2-*c*]pyrimidine (**76**),[61] although no proof of structure was offered. Treatment of the β-(pyrimidin-6-ylamino)propionic acid (**77**) with acetic anhydride, however, has been shown to yield compound **78** by rearrangement.[63]

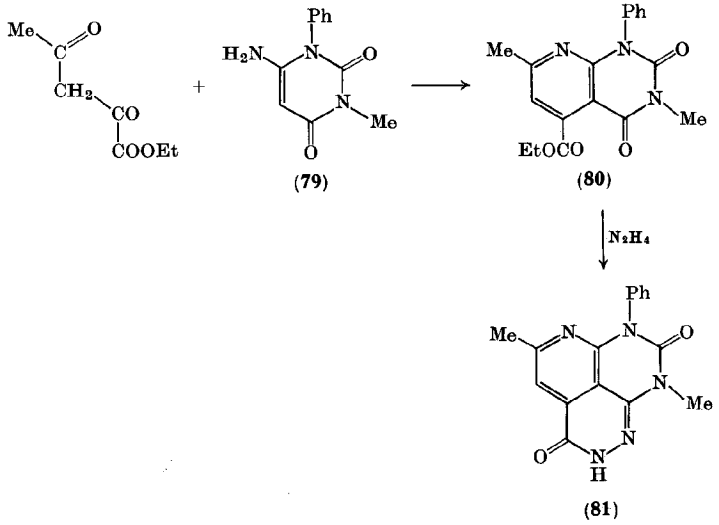


(76) (77) (78)

vii. Acyl pyruvates. As in previous cases of unsymmetrical carbonyl compounds, the most reactive carbonyl (i.e., the pyruvate ketone) undergoes reaction at the pyrimidine nucleus, leading to 5-ethoxycarbonyl derivatives.[53, 54, 64–66] Ethyl pyruvate and 6-amino-3-methyl-1-phenyluracil (**79**) yielded the pyrido[2,3-*d*]pyrimidine (**80**) when treated with phosphorus pentoxide. The orientation of the 5-ethoxycarbonyl group has been proved by the conversion of the pyrido[2,3-*d*]pyrimidine (**80**) into the penta-azaphenalene (**81**) on treatment with hydrazine hydrate.

viii. Acetylenic ketones. 6-Aminouracil has been shown to react with propargyl aldehyde, 3-phenylprop-1-yn-3-one, or halogen acid adducts of acetylenic ketones such as 1-chlorobut-1-en-3-one to yield pyrido[2,3-*d*]pyrimidines.[67] Thus, 3-phenylprop-1-yn-3-one and

[63] T. Ueda and J. J. Fox, *J. Org. Chem.* **29**, 1762 (1964).
[64] M. Ridi, P. Papini, and S. Checchi, *Ann. Chim.* (*Rome*) **46**, 428 (1956).
[65] M. Ridi and S. Checchi, *Ann. Chim.* (*Rome*) **47**, 728 (1957).
[66] S. Fatutta, *Gazz. Chim. Ital.* **93**, 576 (1963).
[67] H. Pasedach and M. Seefelder, German Patent No. 1040,040 (1958); *Chem. Abstr.* **55**, 6507 (1961).

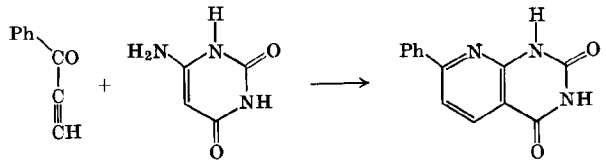


(79) (80) (81)

6-aminouracil yielded 7-phenylpyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**82**).

b. *Route (ii) Syntheses.* This mode of synthesis is typified by the reaction of an active methylene compound, containing an adjacent functional group capable of cyclization with 5-acyl- or 5-ethoxycarbonyl-4-aminopyrimidines. Cyclizations of this type are of importance because, although the required pyrimidines are generally more difficult to prepare than those encountered in the previous section, the pyrido[2,3-*d*]pyrimidines which are obtained need not be substituted in the pyrimidine ring.

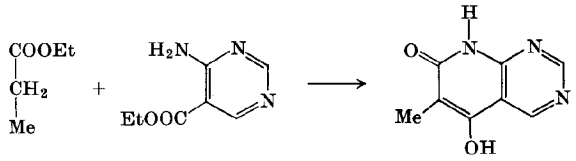
4-Amino-5-ethoxycarbonylpyrimidine[68] and the 2-methyl derivative[69] have been shown to undergo reaction with α-methylene



(82)

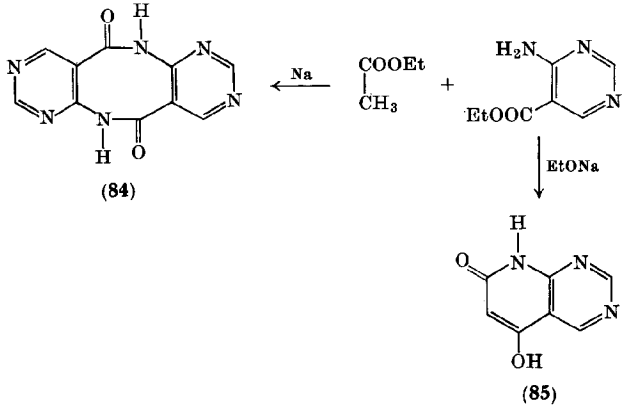
[68] H. Bredereck, F. Effenberger, E. Henseleit, and E. H. Schweizer, *Chem. Ber.* **96**, 1868 (1963).
[69] A. Dornow and E. Hinz, *Chem. Ber.* **91**, 1834 (1958).

esters,[68, 69] ketones,[68] and nitriles[68] to yield 5-hydroxypyrido[2,3-*d*]-pyrimidines variously substituted at the 6- and 7-positions. 4-Amino-5-ethoxycarbonylpyrimidine and ethyl propionate, for example, yield 5-hydroxy-6-methylpyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**83**) when heated together with metallic sodium.



(**83**)

Ethyl acetate, however, yielded the diamide (**84**) under similar conditions, and the pyrido[2,3-*d*]pyrimidine (**85**) was obtained only when sodium ethoxide was used as the catalyst.[68]



(**84**)

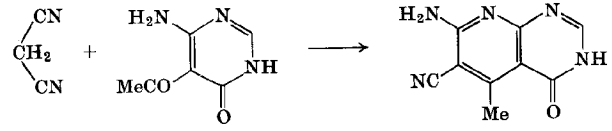
(**85**)

A further convenient synthesis is that developed by Taylor and Garcia[70] who showed that pyrido[2,3-*d*]pyrimidines (**86** and **87**) were obtained by the action of malononitrile on 5-acetyl-4-aminopyrimidin-6(1*H*)-one or 4-amino-5-benzoyl-1-methylpyrimidin-6(1*H*)-one.

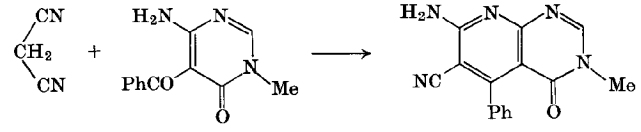
Phenylacetonitrile, ethyl cyanoacetate, and cyanoacetamide failed to yield pyrido[2,3-*d*]pyrimidines.[70]

c. *Route (iii) Syntheses.* In contrast to the previous syntheses which have been described, pyrido[2,3-*d*]pyrimidines prepared by this route

[70] E. C. Taylor and E. E. Garcia, *J. Org. Chem.* **29**, 2116 (1964).



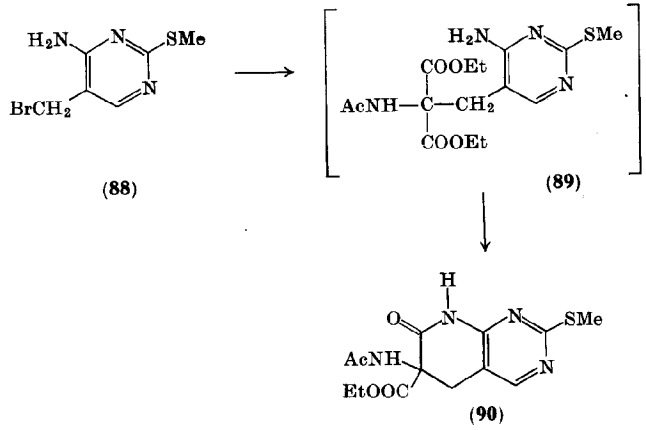
(**86**)



(**87**)

are not completely aromatic compounds, or tautomers of aromatic compounds, and are obtained by cyclization of an aliphatic propionyl derivative.

Alkylation of diethyl acetamidomalonate with the bromomethylpyrimidine (**88**) yielded 6-acetamido-6-ethoxycarbonyl-5,6-dihydro-2-methylthiopyrido[2,3-*d*]pyrimidin-7(8*H*)-one (**90**), via the cyclization of the intermediate ester (**89**).[71]



(**88**)

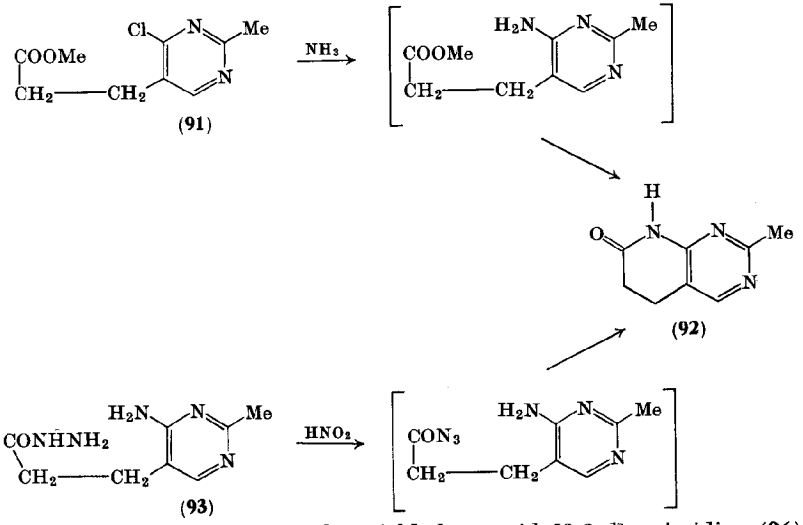
(**89**)

(**90**)

Similar ready cyclizations of propionyl derivatives are exemplified by the cyclization of the ester (**91**) to yield the pyrido[2,3-*d*]pyrimidine

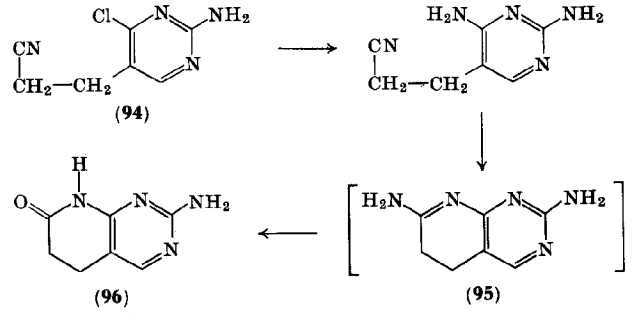
[71] B. Blank and W. T. Caldwell, *J. Org. Chem.* **24**, 1137 (1959).

(92) when treated with ammonia.[72, 72a] This pyrido[2,3-*d*]pyrimidine (92) was also obtained by the action of nitrous acid on the hydrazide (93).



(91) (92) (93)

The propionitrile (94) also yielded a pyrido[2,3-*d*]pyrimidine (96) when treated with ammonia or methylamine, the intermediate amidine (95) undergoing hydrolysis during the reaction.[73] Amination was shown to be the rate-determining stage.



(94) (96) (95)

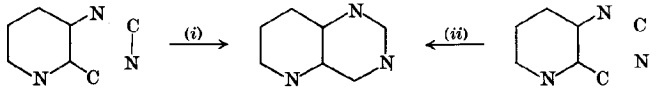
[72] J. Biggs and P. Sykes, *J. Chem. Soc.* p. 1849 (1959).
[72a] L. Suranyi and L. Schuler, German Patent No. 1,100,030 (1961); *Chem. Abstr.* **57**, 2231 (1962).
[73] B. R. Baker and P. I. Almaula, *J. Heterocyclic Chem.* **1**, 263 (1964).

Other 4-aminopyrimidyl-5-propionitriles, obtained by cyanoethylation of the required pyrimidine, have also been converted into pyrido[2,3-*d*]pyrimidines.[74]

B. Pyrido[3,2-*d*]pyrimidines

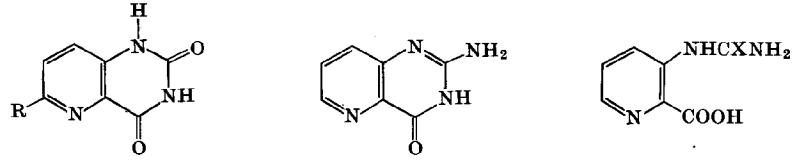
1. *From Pyridines*

The syntheses of pyrido[3,2-*d*]pyrimidines from pyridines utilize a 2,3-disubstituted pyridine and insert the C-2 and N-3 atoms, either previously linked (route *i*) or in separate stages (route *ii*).



a. *Route (i) Syntheses.* As in the case of the pyrido[2,3-*d*]pyrimidines, the first reported pyrido[3,2-*d*]pyrimidines were prepared by an extension of the von Niementowski quinazolone synthesis. Thus, the fusion of 3-aminopicolinic acid with formamide yielded pyrido[3,2-*d*]-pyrimidin-4(3*H*)-one (97)[75, 76] and similar treatment of 3-amino-

(97)



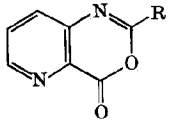
(98) (99) (100)

[74] V. Papesch, U.S. Patent No. 3,235,554 and No. 3,235,555 (1966); *Chem. Abstr.* **64**, 14198 (1966).
[75] C. C. Price and D. Y. Curtin, *J. Am. Chem. Soc.* **68**, 914 (1946).
[76] A. Albert and A. Hampton, *J. Chem. Soc.* p. 505 (1954).

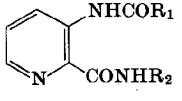
picolinic acid[10,77] or 3-amino-6-methylpicolinic acid[78] with urea gave pyrido[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones (**98**, R = H and R = Me).

The 6-methyl derivative (**98**, R = Me) was an important intermediate in the synthesis of analogs (e.g., **183**) of folic acid.[79,80] Korte[81] has shown that 2-aminopyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**99**) is formed by fusion of guanidine carbonate with 3-aminopicolinic acid and that treatment of the same acid with ammonium thiocyanate or potassium cyanate yields the thioureido and ureido derivatives (**100**, X = S and X = O). In contrast to the pyrido[2,3-*d*]pyrimidine system both of these compounds could be cyclized by heat and the latter (**100**, X = O) is a likely intermediate in the synthesis of the dione (**98**) by the fusion with urea.

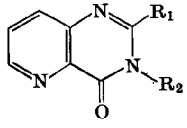
b. *Route (ii) Syntheses.* Pyrido[3,2-*d*][1,3]oxazin-4-ones (**101**) are convenient intermediates which enable 2,3-disubstituted pyrido-[3,2-*d*]pyrimidin-4(3*H*)-ones (**103**) to be prepared in a stepwise manner from 3-aminopicolinic acid.[23] Aliphatic and aromatic amines, am-



(**101**)



(**102**)



(**103**)

monia, hydroxylamine, and hydrazine all underwent an immediate reaction with both 2-methyl- (**101**, R = Me) and 2-phenyl-pyrido-[3,2-*d*][1,3]oxazin-4-one (**101**, R = Ph). In the 2-phenyl series the product was invariably a 3-benzamidopicolinamide (**102**, R_1 = Ph) and cyclization was effected by dissolution in phosphoryl chloride. In the 2-methyl series, hydroxylamine, hydrazine, and ammonia all yielded the pyridopyrimidones (**103**, R_1 = Me, R_2 = OH, NH_2, or H), by reactions carried out at room temperature, without the need for prior isolation of the intermediate amide. A number of aromatic amines also

[77] G. H. Hitchings and R. K. Robins, U.S. Patent No. 2, 686,781, (1954); *Chem. Abstr.* **50**, 1932 (1956).

[78] V. Oakes and H. N. Rydon, British Patent No. 838,015 (1960); *Chem. Abstr.* **54**, 24821 (1960).

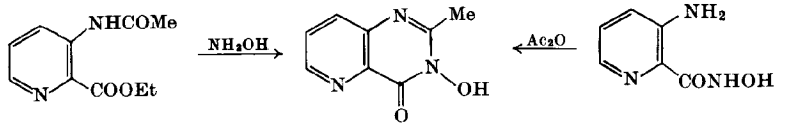
[79] V. Oakes, H. N. Rydon, and K. Undheim, *J. Chem. Soc.* p. 4678 (1962).

[80] O. D. Bird, V. Oakes, K. Undheim, and H. N. Rydon, *Pteridine Chem., Proc. 3rd Intern. Symp., Stuttgart, 1962*, p. 417 (1964).

[81] F. Korte, *Chem. Ber.* **85**, 1012 (1952).

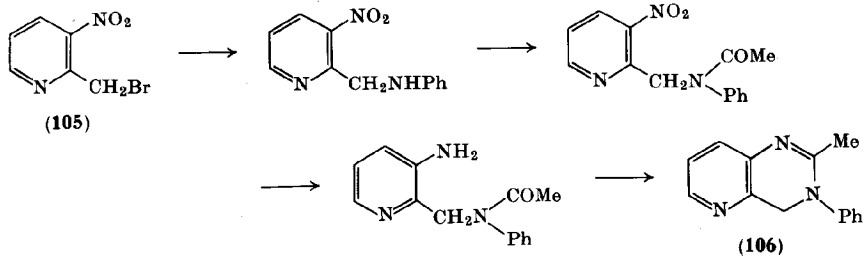
gave pyridopyrimidines directly on treatment with the pyridooxazine (**101**, R = Me) at 150–200°.

The cyclic hydroxamic acid (**104**) obtained by this route had previously been prepared[21] by the two methods illustrated. These exemplify well the variants possible within route (*ii*).



(**104**)

A further stepwise synthesis of this type, in which 2-bromomethyl-3-nitropyridine (**105**) was the starting material, is the only method so far reported which directly produces pyrido[3,2-*d*]pyrimidines without nuclear oxygen substituents (**106**).[82]

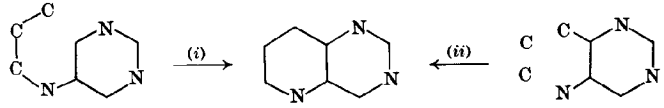


(**105**)

(**106**)

2. *From Pyrimidines*

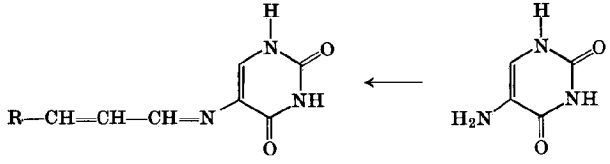
Those syntheses of pyrido[3,2-*d*]pyrimidines in which pyrimidines are the starting materials are completed either by an intramolecular electrophilic cyclization of a pyrimidine with a vacant 4-position (route *i*) or by the addition of the C-5 and C-6 atoms to a 4-substituted-5-aminopyrimidine (route *ii*).



[82] J. Hurst, Ph.D. Thesis, University of London, 1965.

a. *Route (i) Syntheses.* Ring closure reactions of this type are extremely useful in the synthesis of quinolines,[83] and have been used with some success in the preparation of all four 1,x-naphthyridines.[84]

The Doebner–Miller reaction has been extended[85] to the synthesis



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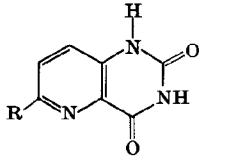
(108)



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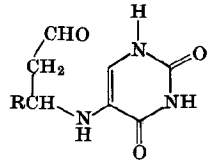
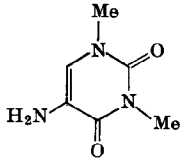
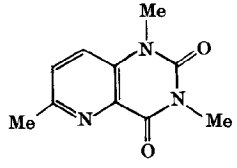


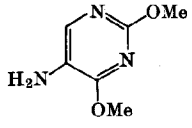
(109)



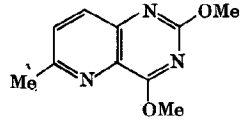
(110)



(111)



(113)



(114)

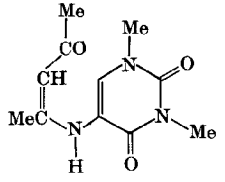
[83] R. C. Elderfield, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 4, p. 1. Wiley, New York, 1957.

[84] M. J. Weiss and C. R. Hauser, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 7, p. 198. Wiley, New York, 1961.

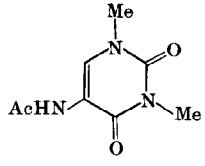
[85] J. Davoll and D. H. Laney, British Patent No. 829,276 (1960); *Chem. Abstr.* **55**, 587 (1961).

of several alkyl-substituted pyrido[3,2-*d*]pyrimidine-2,3(1*H*,3*H*)-diones (**112**) from α,β-unsaturated ketones and 5-aminouracil (**108**).

It was later[86] shown that both *N*- (**110**) and *O*- (**113**) dimethylated 5-aminouracils yielded similar products (**111** and **114**) with crotonaldehyde but that cyclization did not occur with a pyrimidine having fewer electron-donating groups (e.g., 5-amino-pyrimidin-4(3*H*)-one). A further limitation was that 6-arylpyrido[3,2-*d*]pyrimidines could not be synthesized; cinnamaldehyde yielded anils (**107**, R = Ph) rather than the required aminoaldehydes (**109**). Attempts to extend the Combes synthesis[83,84] to this system were unsuccessful.[86] The condensation of the 1,3-dicarbonyl compound with the 5-aminopyrimidine often gave unwanted by-products and even when suitable intermediates were obtained cyclization could not be accomplished. The aminopentenone (**115**), for example, was recovered unchanged or converted into 5-amino-1,3-dimethyluracil (**110**) or its acetyl derivative (**116**) in all attempts at cyclization. A mixture of diethyl malonate and 5-amino-1,3-dimethyluracil yielded the amide (**117**) and the trione (**118**) when heated together, but similar reactions of other 5-aminopyrimidines and diethyl malonate gave no pyridopyrimidines.



(115)



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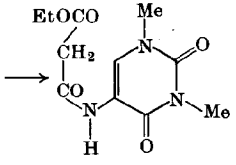
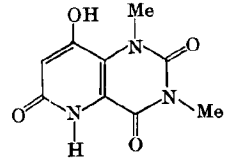
(110) →



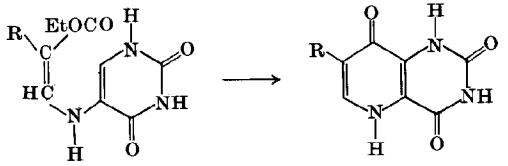
(117)



(118)

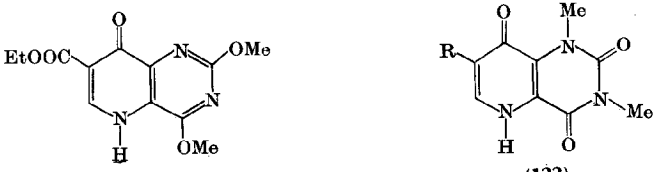
The most satisfactory method[86] involving this type of intramolecular electrophilic cyclization was the thermal ring-closure of aminomethylenemalonates (e.g., **119**, R = COOEt) to yield the pyrido[3,2-*d*]pyrimidine-2,4,8(1*H*,3*H*,5*H*)-trione (**120**, R = COOEt).

[86] W. J. Irwin and D. G. Wibberley, *J. Chem. Soc.* **C**, 1745 (1967).



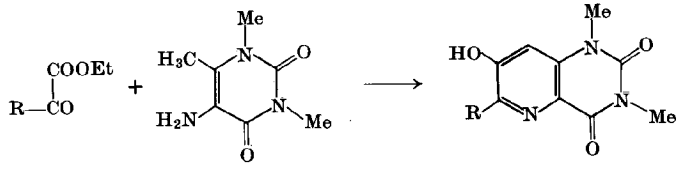
(119) (120)

The methylated 5-aminouracils (**110** and **113**) were also converted into similar aminomethylenemalonates which cyclized to yield the corresponding pyridopyrimidines (**121** and **122**, R = COOEt).



(121) (122)

The aminomethylenemalonate derived from 5-amino-pyrimidin-4(3H)-one was unchanged after a similar period of heating. The cyclization of the corresponding cyanoacetates (e.g., **119**, R = CN) was more difficult, and only that derived from 5-amino-1,3-dimethyluracil (**110**) yielded a pure product (**122**, R = CN).



(123) (124)

b. *Route (ii) Syntheses.* Earlier claims for the formation of quinolines from *o*-toluidines by reaction with glyoxal have been proved incorrect.[87] The formation of pyridopyrimidines (**124**)[88] by the condensation of 5-amino-1,3,4-trimethyluracil (**123**) with α-keto esters such as methyl pyruvate and ethyl mesoxalate or with diethyl oxalate is therefore noteworthy. Of further interest is the preparation by the

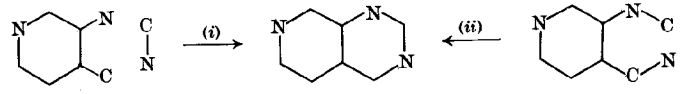
[87] H. E. Baumgarten, H. C. F. Su, and R. P. Barkley, *J. Heterocyclic Chem.* **3**, 357 (1966).

[88] W. Pfleiderer and H. Mosthaf, *Chem. Ber.* **90**, 728 (1957).

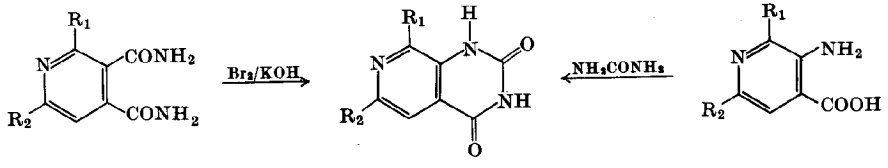
same authors of 6,7-dihydroxypyrido[3,2-*d*]pyrimidine since, excluding the parent compound (**2**), this is the only known pyrido[3,2-*d*]-pyrimidine unsubstituted in the pyrimidine ring.

C. Pyrido[3,4-*d*]pyrimidines

This is the least investigated system and the few known derivatives have been synthesized from 3,4-disubstituted pyridines (routes *i* or *ii*). The first recorded pyridopyrimidine of any system was pyrido[3,4-*d*]-



pyrimidine-2,4(1*H*,3*H*)-dione (**126**, $R_1 = R_2 = H$) prepared by Gabriel and Colman[89] by the Hofmann degradation of cinchomeronamide (**125**, $R_1 = R_2 = H$). The same type of synthesis has been extended to the preparation of 6-methyl- (**126**, $R_1 = H$, $R_2 = Me$)[90] and 6,8-dimethyl-pyrido[3,4-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (**126**, $R_1 = R_2 = Me$).[37, 91] By analogy with the similar route from quinolinamide (Section II,A,2,*h*) pyrido[4,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones are the expected products from cinchomeronamide, but hydrolysis of the products to 3-aminoisonicotinic acids (**127**)[37, 89, 91] or the alternative syntheses (of **126**) from these acids and urea,[89, 91] establish the



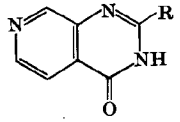
(125) (126) (127)

presence of the pyrido[3,4-*d*]pyrimidine ring system in these compounds. Fusion of acetamide with 3-aminoisonicotinic acid yielded the 2-methyl derivative (**128**, R = Me) in this series, and, as in all the other systems, the fusion with formamide successfully produced pyrido-[3,4-*d*]pyrimidin-4(3*H*)-ones (**128**, R = H, and **129**).

[89] S. Gabriel and J. Colman, *Ber. Deut. Chem. Ges.* **35**, 2831 (1902).

[90] M. J. Reider and R. C. Elderfield, *J. Org. Chem.* **7**, 286 (1942).

[91] I. R. Gelling and D. G. Wibberley, unpublished observations, 1968.



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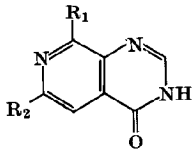
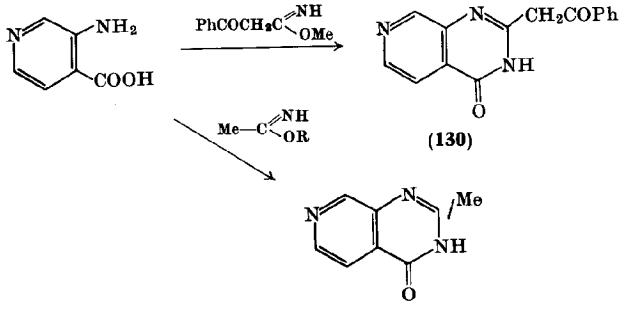


(129)

Reactions having no parallel in any of the other systems of pyridopyrimidine are those syntheses utilizing methyl α-benzoylacetimidate (**130**)[92] and acetimidate esters (**131**).[93]



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(131)

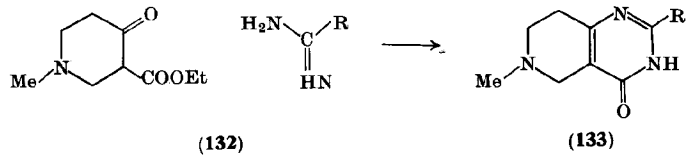
D. Pyrido[4,3-*d*]pyrimidines

The preparations of over two hundred tetrahydro- and octahydropyrido[4,3-*d*]pyrimidines from piperidines or from purely aliphatic starting materials are described in the patent literature. Fully aromatic examples of the system have been prepared from pyridines and pyrimidines.

1. *From Piperidines*

The first recorded pyrido[4,3-*d*]pyrimidine (**133**) was synthesized in 1945[94] by the action of benzamidine on ethyl 1-methylpiperid-4-one-3-carboxylate (**132**). Many more tetrahydro derivatives have been prepared by the similar condensation of various 1,5-substituted

[92] A. de Cat and R. van Pouche, *Compt. Rend. 27th Congr. Intern. Chim. Ind., Brussels*, **3** (1954); *Chem. Abstr.* **50**, 12063 (1956).
[93] W. Ried and J. Valentin, *Ann. Chem.* **707**, 250 (1967).
[94] A. H. Cook and K. J. Reed, *J. Chem. Soc.* p. 399 (1945).

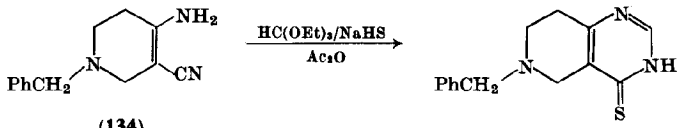


(132)

(133)

piperid-4-one-3-carboxylates with amidines, ureas, thio ureas, and guanidines.[94–96c].

The same amino compounds also underwent reactions with a series of 3-cyano-4-imino- and 3-cyano-4-oxo-piperidines to yield 4-amino-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidines.[96–96c]. A tetrahydropyrido[4,3-*d*]pyrimidine (**135**) was also prepared from 4-amino-1-benzyl-3-cyano-Δ^3-piperidine (**134**)[97,98] by a simple one-step preparation. This method is of general application for the preparation of fused pyrimidines and previous papers in this field are listed by Taylor.[99]



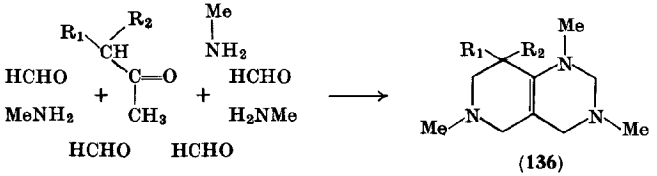
(134)

(135)

2. *From Aliphatic Starting Materials*

8,8-Diaryl-1,3,6-trimethyl-1,2,3,4,5,6,7,8-octahydropyrido[4,3-*d*]-pyrimidines (**136**) were prepared by the reaction between methylamine, formaldehyde, and a 1,1-diarylpropan-2-one in the presence of a basic

[95] G. Ohnacker, U.S. Patent No. 3,186,991 (1965); *Chem. Abstr.* **63**, 4312 (1965).
[95a] G. Ohnacker, U.S. Patent No. 3,306,901 (1967); *Chem. Abstr.* **67**, 73618 (1967).
[96] K. Thomae, French Patent No. M2450 (1964); *Chem. Abstr.* **61**, 8307 (1964).
[96a] K. Thomae, French Patent No. M2798 (1964); *Chem. Abstr.* **62**, 6493 (1965).
[96b] K. Thomae, French Patent No. M2928 (1964); *Chem. Abstr.* **62**, 9150 (1965).
[96c] K. Thomae, Netherlands Patent Appl. 6,400,580 (1966); *Chem. Abstr.* **64**, 5111 (1966).
[97] E. C. Taylor, A. McKillop, and S. Vromen, *Tetrahedron* **23**, 885 (1967).
[98] E. C. Taylor, S. Vromen, R. V. Ravindranathan, and A. McKillop, *Angew. Chem. Intern Ed. English* **5**, 308 (1966).
[99] E. C. Taylor, A. McKillop, and R. N. Warrener, *Tetrahedron* **23**, 891 (1967).

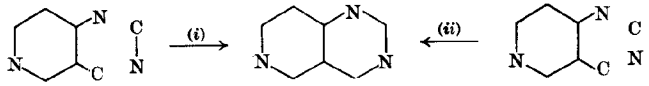


(136)

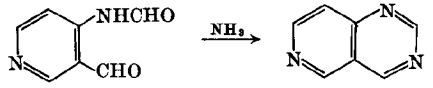
catalyst.[100, 100a] These are the only pyridopyrimidines of any system to have been prepared from aliphatic starting materials, but a one-step synthesis using aliphatic starting materials was successful in the pteridine field.[101]

3. *From Pyridines*

All existing syntheses of pyrido[4,3-*d*]pyrimidines from pyridines build up the pyrimidine ring from a 3-substituted 4-aminopyridine by methods closely similar to those applied for the other systems (routes *i* and *ii*). The preparation of suitable 4-aminopyridines presents some



difficulties; 4-aminonicotinaldehyde, for example, which is potentially the most versatile of such starting materials, has been prepared by a seven-stage route from commercially available compounds.[33] Treatment of 4-formamidonicotinaldehyde (**137**) with methanolic ammonia at 100° then yields pyrido[4,3-*d*]pyrimidine (**4**).[33]



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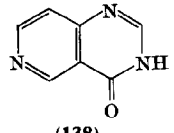


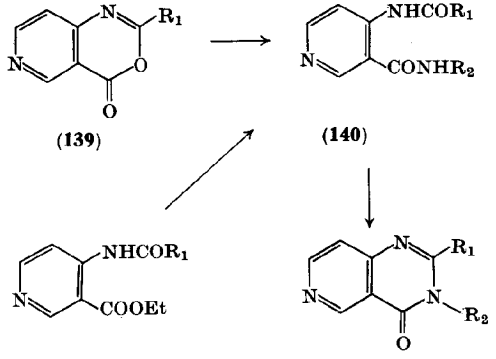
(138)

[100] Hoffmann La Roche and Co., British Patent No. 776,335 (1957); *Chem. Abstr.* **51**, 18015 (1957).

[100a] Hoffmann La Roche and Co., U.S. Patent No. 2,802,826 (1957); *Chem. Abstr.* **52**, 3874 (1958).

[101] E. C. Taylor and C. C. Cheng, *J. Org. Chem.* **24**, 997 (1959).

Pyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**138**) was prepared from either ethyl 4-aminonicotinate[102] or from 4-aminonicotinamide[33] by fusion with formamide. A parallel to the pyrido[3,2-*d*]pyrimidines (cf. Section II,B,1*a*) was demonstrated in the conversion of 2-methylpyrido[4,3-*d*][1,3]oxazin-4-ones (**139**, R_1 = Me) into the corresponding pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones (**142**) on treatment with a number of amines.[103] There were certain limitations to the method in this series, however, and the intermediate diamides (**140**) were more conveniently prepared from the appropriate 4-amidonicotinate (**141**) and



(139) (140)

(141) (142)

the amine. In many cases it was not necessary to isolate the intermediate diamide (**140**); hydroxylamine, for example, gave cyclic hydroxamic acids (**142**, R_2 = OH) directly with six different amidonicotinates. The easier cyclization (**140** → **142**) in this series was accounted for[103] by the superior electrophilicity of the 4-amido carbonyl group.

4. *From Pyrimidines*

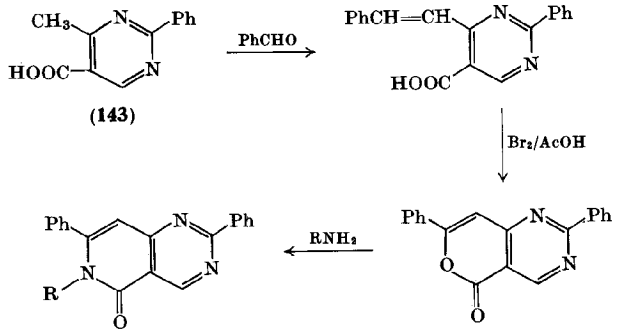
7-Phenylpyrido[4,3-*d*]pyrimidin-5(6*H*)-ones (**145**) have been prepared from 7-phenylpyrano[4,3-*d*]pyrimidin-5(6*H*)-ones (**144**) by treatment with ammonia, hydroxylamine, or hydrazine at room temperature.[104] The utility of the route lies in the rapid preparation of 4-methyl-2-phenylpyrimidine-5-carboxylic acid (**143**) from cheap

[102] E. C. Taylor, R. J. Knopf, J. A. Cogliano, J. W. Barton, and W. Pfleiderer, *J. Am. Chem. Soc.* **82**, 6058 (1960).

[103] A. G. Ismail and D. G. Wibberley, *J. Chem. Soc.* **C**, 2613 (1967).

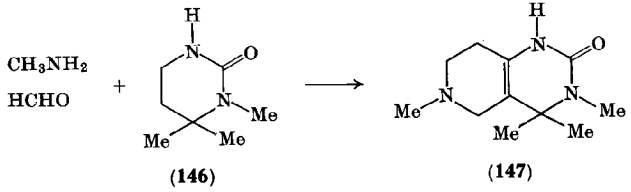
[104] A. G. Ismail and D. G. Wibberley, unpublished observations, 1968.

aliphatic starting materials and the reactivity of a 4-methyl pyrimidine group in condensations with aldehydes.



(143) (144) (145)

The Mannich reaction of 2-oxo- (**146**) and 2-thioxotetrahydropyrimidines yields the hexahydropyrido[4,3-*d*]pyrimidin-2(1*H*)-one (**147**)[105] and the corresponding thione.



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III. Physical Properties

A. General Discussion

The physical properties of the pyridopyrimidines closely resemble those of their nearest *N*-heterocyclic neighbors the quinazolines and the pteridines. Thus, in common with the pteridines,[106] the presence of groups capable of hydrogen-bonding markedly raises the melting point and lowers the solubility.[9, 10] The acid dissociation constants (pK_a values) and ultraviolet absorption spectra of all four parent pyridopyrimidines have been determined by Armarego[33] in a comprehensive study of covalent hydration in these heterocyclic systems. The importance of these techniques in the study of covalent hydration, and

[105] G. Zigeuner, W. Adams, and W. Galatik, *Monatsh. Chem.* **97**, 52 (1966).
[106] A. Albert, J. H. Lister, and C. Pederson, *J. Chem. Soc.* p. 4621 (1956).

the susceptibility of pyridopyrimidines to this phenomenon are well illustrated in the reviews by Albert and Armarego[1] and Perrin.[2]

B. Ultraviolet Absorption Spectra

The pyridopyrimidines possess the same π-electron structure as naphthalene. The electronic transitions between the π-orbitals would therefore be expected to give rise to similar ultraviolet spectra. As in the case of the quinazolines[4] and the pteridines,[6] this has proved to be so.

Calculations have been made, first by a semiempirical treatment[107] due to Parisier and Parr, and to Pople, and then by a simplified version of this method,[108] of the transition energies and intensities of the $\pi \rightarrow \pi^*$ bands in pyridopyrimidines (cf. Table I).

TABLE I

Calculated Values for the Wavelength Maxima (mμ) in the Ultraviolet Spectra of Pyridopyrimidines[a]

Compound	$\pi \rightarrow \pi^*$ transition band		
	1	2	3
Pyrido[2,3-*d*]pyrimidine	300	264	212
Pyrido[3,2-*d*]pyrimidine	300	261	218
Pyrido[3,4-*d*]pyrimidine	307	269	219
Pyrido[4,3-*d*]pyrimidine	295	279	220

[a] G. Favini, I. Vandoni, and M. Simonetti, *Theoret. Chim. Acta* **3**, 418 (1965).

These results were in fair agreement with the experimentally determined values[33] for the parent compounds in nonionic solvents. Additional values for the $n \rightarrow \pi^*$ transitions have been determined for pyrido[3,2-*d*]pyrimidine (345 mμ logϵ 2.07) and for pyrido[4,3-*d*]-pyrimidine (330 mμ, logϵ 2.49).[33]

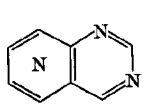
Substituted pyridopyrimidines show the same three principal ($\pi \rightarrow \pi^*$) absorption bands as the parent compounds but with bathochromic shifts which may obliterate bands due to the $n \rightarrow \pi^*$ transitions.

[107] G. Favini, I. Vandoni, and M. Simonetti, *Theoret. Chim. Acta* **3**, 45 (1965).
[108] G. Favini, I. Vandoni, and M. Simonetti, *Theoret. Chim. Acta* **3**, 418 (1965).

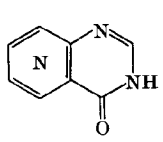
The prediction of the values of such shifts has been considered in closely related *N*-heteroaromatic systems.[109] Ultraviolet absorption maxima have been determined for pyrido[2,3-*d*]pyrimidines,[9, 10, 16, 33, 41–44, 56, 110–112] pyrido[3,2-*d*]pyrimidines,[10, 16, 33, 79, 81] pyrido[3,4-*d*]pyrimidines,[33, 91] and pyrido[4,3-*d*]pyrimidines.[33] The experimentally determined values have been used for studies of covalent hydration, structural assignments,[9, 10, 41, 44] and tautomerism.[10, 113]

C. Infrared Spectra

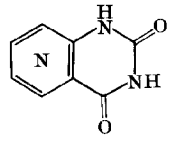
Armarego *et al.*[114] have determined the infrared spectra of the four parent pyridopyrimidines (**148**) in the solid phase as KBr discs, and have compared them with other di-, tri-, and tetraazanaphthalenes. Thirteen in-plane skeletal vibrations and ten CH bending vibrations



(**148**)



(**149**)



(**150**)

are theoretically possible in the 1700–650 cm^{-1} region. Slightly less than this number of bands were actually observed and the results did not provide a simple criterion for distinguishing between predominantly skeletal and predominantly CH vibrations. CH out-of-plane bending vibrations were thought to account for most of the intense bands found in the 1000–650 cm^{-1} region. CH stretching bands in the range 3100–3000 cm^{-1}, and overtone and combination bands in the range 2000–1750 cm^{-1}, were also observed.

[109] S. F. Mason, *in* "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. II, Chapt. 7. Academic Press, New York (1963).
[110] R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.* **78**, 973 (1956).
[111] Y. Inoue and D. D. Perrin, *J. Chem. Soc.* p. 5166 (1963).
[112] G. H. Hitchings, *Drugs, Parasites Hosts, Symp. Middlesex Hosp. Med. School* p. 196 (1962).
[113] A. R. Katritzky and J. M. Lagowski, *Advan. Heterocyclic Chem.* **1**, 341–436 (1963).
[114] W. L. F. Armarego, G. B. Barlin, and E. Spinner, *Spectrochim. Acta* **22**, 117 (1964).

Mason[115] has determined the infrared spectrum of pyrido[3,2-*d*]-pyrimidin-4(3*H*)-one (**149**, N in position 5) in chloroform solution and as a KBr disc and has suggested that the low frequency of the NH band (3389 cm^{-1}) and high frequency of the C=O band (1745 cm^{-1}) in the solution spectra are indicative of a quasi *o*-quinonoid form. The infrared spectra of the four pyridopyrimidin-4(3*H*)-ones (**149**), the four 2,4(1*H*,3*H*)-diones (**150**), and a number of substituted derivatives, have been determined, as Nujol mulls, in these laboratories.[23, 86, 91, 103, 104, 116] The presence of NH stretching absorption in the range 3200–3050 cm^{-1} in these compounds, and of C=O stretching absorption in the range 1730–1690 cm^{-1}, both in the pyridopyrimidinones themselves and in their 1- and 3-methylated derivatives suggest that the oxo structures depicted (**149** and **150**) are the predominant forms in the solid phase. In the absence of solvent shift studies it remains possible that some of the bands also observed in the 1625–1510 cm^{-1} region may also have been at least partly "carbonyl" in character as is the case with pyridin-4-ones[113] and quinolin-4-ones.[113]

D. Nuclear Magnetic Resonance Spectra

Nuclear magnetic resonance spectra of all four parent compounds have been measured and analyzed.[117] The powerful potentialities of NMR as a tool in the study of covalent hydration,[2] tautomerism,[118] or protonation have, however, as yet received no consideration for the pyridopyrimidines. NMR spectra have been used to distinguish between pyrido[3,2-*d*]pyrimidines and isomeric *N*-bridgehead compounds such as pyrimido[1,2-*a*]pyrimidines[44] and in several other structural assignments [44, 56, 60, 125] (cf. **74** and **75**).

The NMR spectral parameters of a number of pyridopyrimidines are shown in Table II.

The signal from H-4 in the parent compounds underwent a greater downfield shift than that from H-2 when the solvent polarity was increased ($CDCl_3 \rightarrow Me_2CO \rightarrow$ DMSO).[117] This was ascribed to the counterbalancing effect of preferential solvation at the N-1 position.

The ring protons of the pyrimidinones and pyrimidine diones would

[115] S. F. Mason, *J. Chem. Soc.* p. 4874 (1957).
[116] W. J. Irwin and D. G. Wibberley, unpublished observations, 1968.
[117] W. L. F. Armarego and T. J. Batterham, *J. Chem. Soc.* **B**, 750 (1966).
[118] R. F. M. White, *in* "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. II, Chapt. 9. Academic Press, New York, 1963.

TABLE II

NUCLEAR MAGNETIC RESONANCE SPECTRA OF PYRIDOPYRIMIDINES[a,b,c,d]

(151) (152) (153)

Compound No.	N-Position	R	Solvent	Chemical shift (τ value) H-2	H-4	H-5	H-6	H-7	H-8	CH_3	Coupling constant (cps) $J_{5,6}$	$J_{6,7}$	$J_{7,8}$	Other J values
151	5		$CDCl_3$	0.55	0.30	—	0.88	2.15	1.60	—	—	4.1	8.3	0.8 (4, 8); 1.7 (6, 8)
152	5	H	TFA[e]	0.95	—	—	0.67	1.42	0.80	—	—	5.0	8.5	1.5 (6, 8)
152	5	CH_3	TFA	—	—	—	0.70	1.50	1.00	6.95	—	6.0	8.0	1.5 (6, 8)
153	5	H	TFA	—	—	—	1.0	1.53	1.2	—	—	5.5	9.0	1.5 (6, 8)
153	5	CH_3	TFA	—	—	—	1.07	1.27	1.20	6.12 6.3	—	6.0	9.0	1.5 (6, 8)
151	6		$CDCl_3$	0.46	0.38	0.53	—	1.00	2.08	—	—	—	5.8	0.7 (4, 8); 0.8 (5, 8)
152	6	H	TFA	0.81	—	0.11	—	0.80	1.48	—	—	—	7.0	—
152	6	CH_3	TFA	—	—	0.15	—	0.80	1.47	6.94	—	—	7.0	—
153	6	H	TFA	—	—	0.48	—	1.14	2.06	—	—	—	7.0	—
151	7		$CDCl_3$	0.43	0.42	2.21	1.15	—	0.45	—	5.8	—	—	—
152[f]	7	H	TFA	1.23	—	1.49	—	—	—	6.77 7.02	—	—	—	—
153[f]	7	H	TFA	—	—	1.80	—	—	—	6.95 7.05	—	—	—	—
151	8		$CDCl_3$	0.43	0.42	1.56	2.28	0.67	—	—	8.3	4.2	—	1.9 (5, 7)
152	8	H	TFA	1.13	—	0.50	1.77	0.73	—	—	8.0	6.0	—	1.5 (5, 7)
153	8	H	TFA	—	—	0.77	2.11	1.05	—	—	8.0	6.0	—	1.5 (5, 7)
153	8	CH_3	TFA	—	—	0.70	2.14	1.17	—	6.02 6.34	8.0	6.0	—	1.5 (5, 7)
153	8	CH_3	$CDCl_3$	—	—	1.57	2.80	1.33	—	6.34 6.57	8.0	6.0	—	2.0 (5, 7)

[a] Measured at 60 Mc/sec.
[b] I. R. Gelling and D. G. Wibberley, unpublished observations, 1968.
[c] A. G. Ismail and D. G. Wibberley, *J. Chem. Soc.* **C**, 2613 (1967).
[d] W. L. F. Armarego and T. J. Batterham, *J. Chem. Soc.* **B**, 750 (1966).
[e] Trifluoroacetic acid.
[f] 6,8-Dimethyl derivative.

be expected to show an upfield shift in comparison with the parent compounds. This is seen to be so (cf. Table II) when deuterochloroform was used as the solvent. Protonation at the pyridine ring nitrogen with trifluoroacetic acid as solvent caused a powerful deshielding of the pyridine protons.

E. Mass Spectra

The mass spectra of a number of pyridopyrimidines have been determined in these laboratories.[91,104,116] Pyridopyrimidin-4(3*H*)-ones showed features in their spectra common to the fragmentation patterns of other *N*-heterocyclic compounds[119] and more particularly

SCHEME 1. Fragmentation pattern of pyrido[3,2-*d*]pyrimidin-4(3*H*)-one.

[119] G. Spiteller, *Advan. Heterocyclic Chem.* **7**, 301 (1966).

to the quinazolin-4(3*H*)-ones[120] and pteridones.[121] Thus, the mass spectrum of pyrido[3,2-*d*]pyrimidin-4(3*H*)-one (Fig. 1) shows the strong molecular ion and *m*/2*e* peak characteristic of this type of compound.[119] The degradation pathway shown in Scheme 1 was confirmed by the presence of metastable ions.

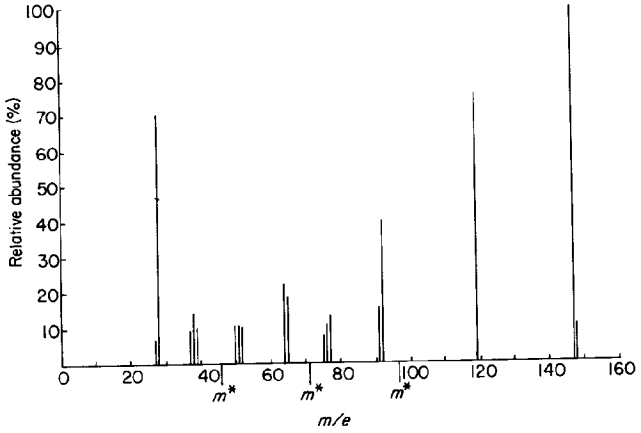
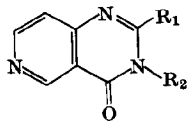
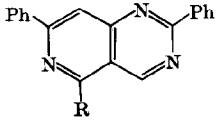


FIG. 1. Mass sprectrum of pyrido[3,2-*d*]pyrimidin-4(3*H*)-one. *m*/2*e* = 73.5.

A series of 2,3-disubstituted pyrido[4,3-*d*]pyrimidin-4(3*H*)-ones (**154**) showed more complicated fragmentation patterns. Here again, however, strong molecular ions were invariably present and *m*/2*e* peaks were common, as were M-1 peaks. The nature of the group R_1



(**154**)



(**155**)

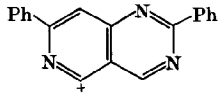
was an important factor which influenced the fragmentation pattern. 2-Furylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one (**154**, R_1 = furyl, R_2 = H,) showed six different primary breakdown peaks originating from the molecular ion. These corresponded to the loss (in decreasing order of probability) of H·, C_4H_3O, ·CN, CO, HCN, C_4H_3O·, and HCNO.

120 T. J. Batterham, A. C. K. Triffet, and J. A. Wunderlich, *J. Chem. Soc.* **B**, 892 (1967).

121 T. Goto, A. Tatematsu, and S. Matsuura, *J. Org. Chem.* **30**, 1844 (1965).

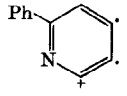
In three of the compounds (**154**, R_2 = H) examined the commonest loss from the molecular ion was the cyanide R_1CN to give the most predominant ion at *m*/*e* = 120 in each case. The M-O peak (M-16), was observed in cyclic hydroxamic acids (**154**, R_2 = OH).

In a series of 2,7-diphenyl 5-substituted pyrido[4,3-*d*]pyrimidines (**155**, R = OH, OEt, Cl, SH, $NHNH_2$) the molecular ions and peaks for the expected phenyl degradation at 65, 63, 52, 51, 50, and 39 were all generally strong. Here again peaks were visible for *m*/2*e* ions and for M-1 and PhCN ions. The variations in the group R affected the breakdown pattern, but ions for *m*/*e* = 282 (**156**) and *m*/*e* = 152 (**157**) were common.



(**156**)

m/*e* = 282



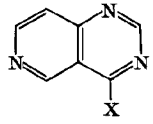
(**157**)

m/*e* = 152

IV. Chemical Properties

A. Nucleophilic Substitution

A large number of nucleophilic substitution reactions involving interconversions of pyridopyrimidines have been reported, the majority of which involve substituents in the pyrimidine ring. This subject has been reviewed previously in an earlier volume in this series which dealt with the theoretical aspects of nucleophilic reactivity in azines,[3] and so only a summary of the nucelophilic displacements of the substituent groups will be given here. In general, nucleophilic substitutions occur most readily at the 4-position of pyrido-



(**158**)

pyrimidines, as is the case with pyrimidines[3] and quinazolines,[3] and this tendency has been explained on theoretical grounds.[3,36] The relative reactivities of the various pyridopyrimidines to nucleophilic attack have been examined by Shepherd and Fedrick,[3] and they conclude that the order of reactivity for a 4-substituent is [4,3-*d*] ≥ [2,3-*d*] > [3,4-*d*] ≥ [3,-2-*d*]. Thus, the pyrido[4,3-*d*]pyrimidine (**158**) is the most reactive compound of the series.

1. *Hydroxy Compounds*

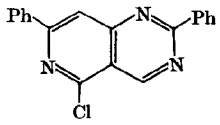
Chlorodehydroxylation with phosphoryl chloride[9, 11, 13, 35, 36, 49, 50] and thionation with phosphorus pentasulfide[9, 11, 48, 50, 102] have been achieved with reactive pyridopyrimidines (e.g., pyrido[2,3-*d*]-pyrimidines) to yield the corresponding chloro or thioxo compounds. With the less-reactive pyrido[3,2-*d*]pyrimidines direct thionation failed,[107] and conversion to chloro derivatives was effected only when phosphorus pentachloride or tertiary amines were added.[10, 56, 78, 100, 100a, 110, 122–124] Thionyl chloride and dimethylformamide have also been useful for the preparation of 7-chloropyrido[2,3-*d*]pyrimidines.[56, 59]

2. *Chloro Compounds*

Chloropyridopyrimidines readily undergo amination reactions with ammonia,[9–11, 13, 36, 41, 48, 50, 78, 110, 122, 123, 126, 127] aliphatic amines,[9–11, 13, 48, 50, 110, 126, 127] and aromatic amines[9, 11, 48, 50, 110, 122] to yield mono- or diaminopyridopyrimidines or 4-amino-2-chloro derivatives. Selective replacement of chloro substituents, however, was not achieved with the reaction of dimethylamine and 2,4-dichloropyrido-[2,3-*d*]pyrimidine.[110] Thionation reactions by means of thiourea,[10, 36, 110, 122] hydrosulfide ion,[9, 13, 48, 50, 56] sodium ethyl sulfide,[10] replacement by alkoxide,[10, 13, 35, 36, 50] and hydrolysis[9, 10, 13, 50] to regenerate the pyridopyrimidone all take place readily. Reductive dehalogenation[10] to yield pyrido[3,2-*d*]pyrimidine (**2**) has been claimed but disputed.[33]

A chloro group in the 5-position in a pyrido[4,3-*d*]pyrimidine proved to be labile,[104] compound **159** being readily converted into the 5-hydrazino, oxo, ethoxy, and thioxo derivatives.

[122] G. H. Hitchings and R. K. Robins, U.S. Patent No. 2,686,781 (1954); *Chem. Abstr.* **50**, 1932 (1956).
[123] V. Oakes and H. N. Rydon, U.S. Patent No. 2,924,599 (1960); *Chem. Abstr.* **54**, 9964 (1960).
[124] Wellcome Foundation, British Patent No. 755,225 (1956); *Chem. Abstr.* **51**, 4445 (1957).
[125] H. C. Scarborough, U.S. Patent No. 3,139,432 (1964); *Chem. Abstr.* **61**, 7024 (1964).
[126] G. Ohnacker, U.S. Patent No. 3,248,395 (1966); *Chem. Abstr.* **65**, 3888 (1966).
[127] Wellcome Foundation, Netherlands Patent No. 6,600,213 (1966); *Chem. Abstr.* **65**, 15396 (1966).



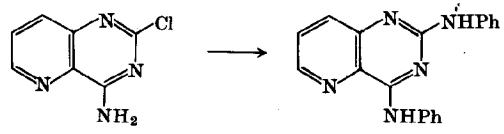
(**159**)

3. *Thio Compounds*

Aminations of pyridopyrimidine-2,4(1*H*,3*H*)-dithiones usually yield 4-aminopyridopyrimidine-2(1*H*)-thiones; ammonia,[9–11, 13, 48, 91, 110, 122, 128] aliphatic,[11, 90, 91, 128] and aromatic amines[11, 90, 128] have been used. Desulfurization with Raney nickel,[9–11, 36, 41, 56, 110, 129] oxidation of methylthio compounds to the corresponding sulfones,[16] and conversion into the parent pyridopyrimidone by means of hydrogen peroxide[54] or chloroacetic acid[41, 66, 102] have been reported. This latter reaction also causes ring-opening in certain cases[102] (see Section IV,C,2).

4. *Amino Compounds*

Hydrolyses of aminopyridopyrimidines to the corresponding pyridopyrimidones by means of acid,[10, 130] base,[110, 130] and nitrous acid[41, 130, 131] have been reported. 4-Amino compounds are stable to nitrous acid, but are much more labile than the 2-amino derivatives toward acid- or base-catalyzed hydrolysis.[130] The aminochloro-pyrido[2,3-*d*]pyrimidine (**160**) has been converted into the 2,4-dianilino analog (**161**) by reaction with aniline.[110]



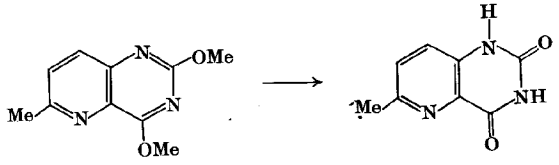
(**160**) (**161**)

[128] K. Thomae, Netherlands Patent No. 6,602,499 (1966); *Chem. Abstr.* **65**, 8932 (1966).
[129] G. H. Hitchings and B. S. Hurlbert, Belgian Patent No. 655,138 (1963); *Chem. Abstr.* **64**, 15896 (1966).
[130] R. B. Trattner, G. B. Elion, G. H. Hitchings, and D. M. Sharefkin, *J. Org. Chem.* **29**, 2674 (1964).
[131] V. Papesch, U.S. Patent No. 3,275,634 (1966); *Chem. Abstr.* **65**, 18601 (1966).

Ureido[132] and benzamido derivatives[79] have been prepared, and a 6-amino group in a pyrido[3,2-*d*]pyrimidine can be diazotized and reduced.[42]

5. *Alkoxy Compounds*

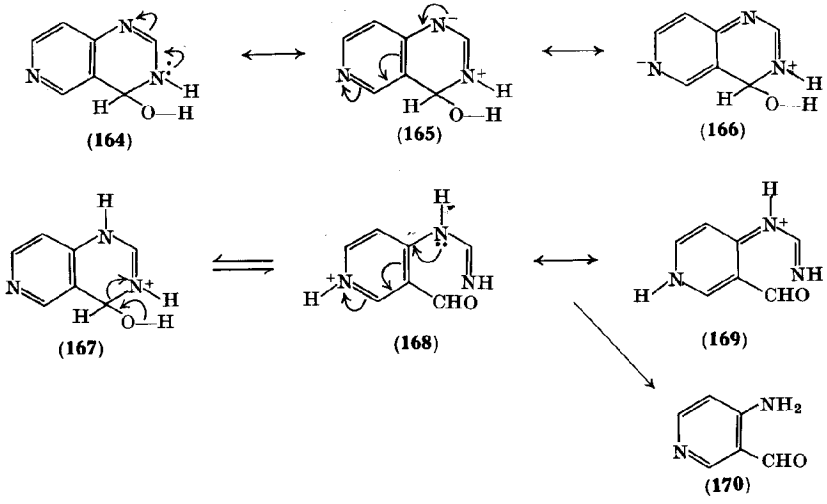
Hydrolysis of the dimethoxypyrido[3,2-*d*]pyrimidine (**162**) to the dione (**163**) has been reported.[86]



(**162**) (**163**)

B. Covalent Hydration

In common with other fused pyrimidines, the pyridopyrimidines are susceptible to the nucleophilic addition of water across the 3,4-bond.[33, 111, 133, 134] This is the phenomenon of covalent hydration which has been adequately reviewed by Albert and Armarego[1] and



(**164**) (**165**) (**166**)

(**167**) (**168**) (**169**) (**170**)

132 V. Papesch, U.S. Patent No. 3,296,447 (1967); *Chem. Abstr.* **66**, 6163 (1967).
133 Y. Inoue, *Tetrahedron* **20**, 243 (1964).
134 D. D. Perrin and Y. Inoue, *Proc. Chem. Soc.* p. 342 (1960).

Perrin[2] in an earlier volume of this series. Worthy of note at this stage, however, is the fact that the location of the nitrogen atom of the pyridine ring has a considerable bearing on the ease of formation and stability of the covalent hydrate.[33] Pyrido[4,3-*d*]pyrimidine (**3**), which decomposes in 4 minutes at pH = 2 to yield 4-aminonicotinaldehyde (**170**), is the least stable pyridopyrimidine. This instability is attributed to resonance stabilization of the hydrate (**164** ↔ **165** ↔ **166**) with respect to the anhydrous compound, and ring-chain tautomerism (**167** ⇌ **168**) favoring ring-opening due to stabilization of the amidine (**168** ↔ **169**).

C. Ring-Opening Reactions

1. *Acid Hydrolysis*

The parent compounds undergo facile hydrolysis to aminoaldehydes subsequent to the covalent hydration and reversible ring-opening as described above for pyrido[4,3-*d*]pyrimidines (Section IV, B). 2-(3-Pyridyl)pyrido[2,3-*d*]pyrimidine undergoes hydrolysis to yield 2-aminonicotinaldehyde and nicotinamide when treated with N—HCl under reflux for 3 hours.[38] This mechanism also probably involves a covalent hydrate. 2-Methylpyrido[4,3-*d*]pyrimidin-4(3H)-one, although much more stable than the parent compound, is readily hydrolyzed with dilute acid,[103] whereas the isomeric compounds from the other three systems are stable under such conditions.

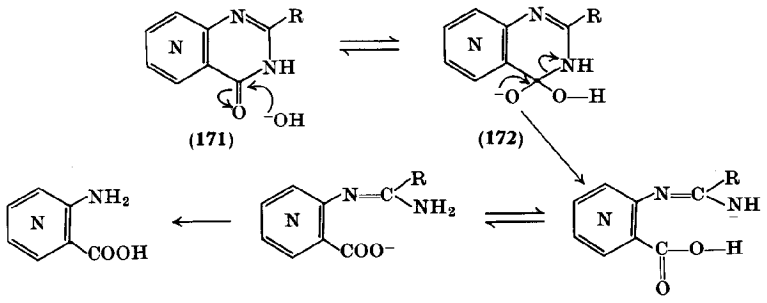
Further substitution with amino or oxo groups increases the stability of the ring. Thus, pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**51**) gave a 12% yield[35] of 2-aminopyridine after treatment with concentrated H_2SO_4 for 25 minutes at 280°, and 2-aminopyrido-[2,3-*d*]pyrimidin-4(3*H*)-one (**57**, R = H) was recovered unchanged after similar treatment. Indeed, conditions similar to these have been used for the preparation of pyridopyrimidines (see Section II, A, 2, *i*). 6,8-Dimethylpyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione was converted quantitatively into its hydrochloride and did not undergo ring-opening with concentrated HCl (100°/24 hours).[91]

2. *Alkaline Hydrolysis*

No detailed studies of ring-opening by basic reagents have been reported in the literature, but here again evidence suggests that

increasing the number of hydroxy groups in the molecule renders hydrolysis more difficult. Thus, 6,8-dimethylpyrido[3,4-*d*]pyrimidine-2,4(1*H*,3*H*)-dione was unaffected by treatment with NaOH (5%) for 2 hours at 50°, but underwent hydrolysis to yield 3-amino-2,6-dimethylisonicotinic acid when heated under reflux with NaOH (30%) for 17 hours.

The mechanism of ring-opening of pyridopyrimidin-4(3*H*)-ones under alkaline conditions is presumably as follows:



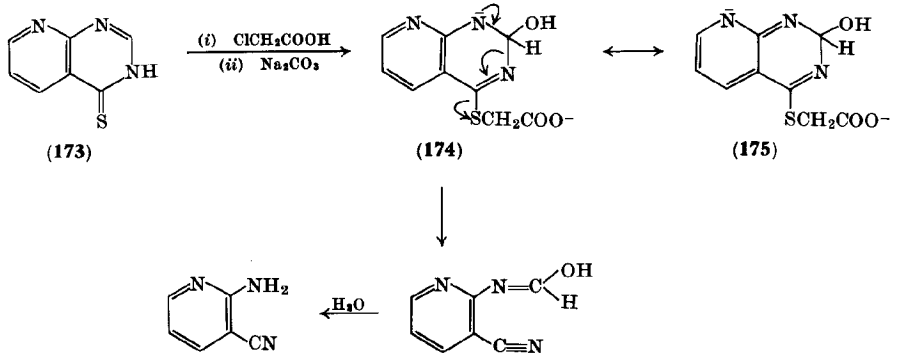
(171) (172)

Factors that affect the rate-determining step (**171** → **172**) will influence the overall rate of reaction. A stronger nucleophile, such as hydrazine,[23] is certainly more efficient than hydroxide, but no studies have been reported on the alternative variation of the electrophilicity of the 4-carbonyl group. Ring-opening may occur at either the 3,4-[35, 91, 135, 136] or 1,2-bonds[53, 65, 137] in pyridopyrimidine-2,4(1*H*,3*H*)-diones although the latter appears less probable. Additional factors, such as the cyclization of the first-formed ring-opened products with a 5-ethoxycarbonyl group are often important.[53]

E. C. Taylor and his co-workers have demonstrated an important principle in the ring-opening of pyridopyrimidines and other fused pyrimidine systems to *o*-aminonitriles.[102] They have demonstrated that based-catalyzed cleavage of a 4-substituted pyrimidine will occur provided that (*a*) the anion formed by the attack by the base at the 2-position can be stabilized by appropriate structural features in the remainder of the molecule and (*b*) that the substituent attached to the 4-position is capable of departure with its bonding pair of electrons in

[135] R. C. Elderfield and M. Wharmby, *J. Org. Chem.* **32**, 1638 (1967).
[136] J. R. Geigy, Belgian Patent No. 609,184 (1962), *Chem. Abstr.* **57**, 15105 (1962).
[137] R. Vonderwahl, U.S. Patent No. 3,035,061 (1962); *Chem. Abstr.* **57**, 11213 (1962).

an irreversible cleavage stage. Thus, pyrido[2,3-*d*]pyrimidine-4(3*H*)-thione (**173**), on treatment with chloroacetic acid and sodium carbonate, gave a mixture of starting material, 2-aminonicotinonitrile, 2-aminonicotinamide, and some pyrido[2,3-*d*]pyrimidin-4(3*H*)-one. In this case the 4-carboxymethylthio anion is a good leaving group and the anion (**174**) may be stabilized by the delocalization of the negative charge to the pyridine ring nitrogen atom (**175**).



(173) (174) (175)

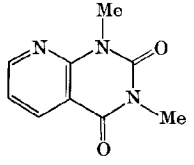
A similar delocalization of charge which stabilizes the relevant intermediate occurs in 4-mercaptopteridine and pyrido[4,3-*d*]-pyrimidine-4(3*H*)-thione. Both these compounds are cleaved under similar conditions. Such a delocalization is not possible with either pyrido[3,2-*d*]- or pyrido[3,4-*d*]pyrimidine-4(3*H*)-thione and although the latter compound could not be prepared, the pyrido[3,2-*d*]pyrimidine was quite stable under these conditions.

D. Electrophilic Substitution

No example of electrophilic substitution at ring carbon atoms has been reported.

Electrophilic substitution at ring nitrogen atoms has been limited to protonation and *N*-alkylation of the anion derived from a pyridopyrimidinone.[10, 35, 53, 64, 65, 88, 91] Thus, the sodium salt of pyrido-[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione and dimethylsulfate yield the 1,3-dimethyl derivative (**176**).

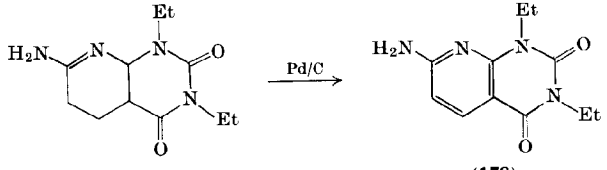
The stability constant for the nickel chelate of pyrido[2,3-*d*]-pyrimidine-4(3*H*)-one has been measured.[76]



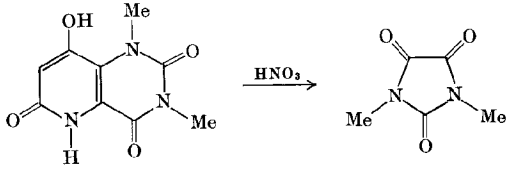
(176)

E. Oxidation

Oxidations of pyridopyrimidines are rare, but the covalent hydrates of the parent compounds undergo oxidation with hydrogen peroxide to yield the corresponding pyridopyrimidin-4(3*H*)-ones.[33] Dehydrogenation of dihydropyrido[2,3-*d*]pyrimidines by means of palladized charcoal, rhodium on alumina, or 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) to yield the aromatic derivatives have been reported.[138] Thus, 7-amino-5,6-dihydro-1,3-diethylpyrido[2,3-*d*]-pyrimidine-2,4(1*H*,3*H*)-dione (**177**) is aromatized (**178**) when treated with palladized charcoal in refluxing toluene for 24 hours.



(177) (178)



(179) (180)

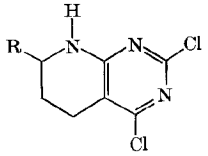
The trione (**179**) yields 1,3-dimethylparabanic acid (**180**) when treated with nitric acid.[86]

F. Reduction

In contrast to the reductive dehalogenation of 2,4-dichloropyrido-[3,2-*d*]pyrimidine,[10] 2,4-dichloropyrido[2,3-*d*]pyrimidine[10] and its 6-

138 V. Papesch, U.S. Patent No. 3,272,816 (1966); *Chem. Abstr.* **61**, 7024 (1964).

methyl analog[36] underwent ring-reduction when treated with Adam's catalyst and hydrogen. A dichlorotetrahydropyrido[2,3-*d*]pyrimidine was obtained for which the structure (**181**) was proposed.



(181)

Hydrogenation of the pyridine ring in the reduction of 2-amino-pyrido[2,3-*d*]pyrimidin-4(3*H*)-one was proved by synthesis.[39]

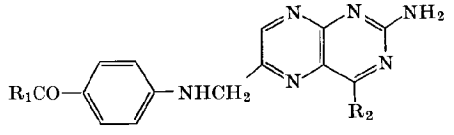
Distillation of pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione with zinc dust yielded 1,3,4-triazaindene.[10]

G. Reactive Methyl Groups

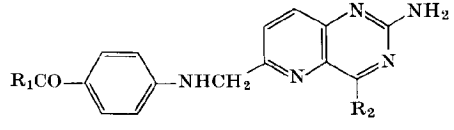
Little data is available, but methyl groups α and γ to ring nitrogens appear to be activated. 2-Methyl and 6-methyl substituents in pyrido[3,2-*d*]pyrimidines undergo bromination[36, 79, 123] and oxidative decarboxylation,[23] and form styryl compounds.[23] The 6-methyl group in pyrido[2,3-*d*]pyrimidines could not be brominated.[78]

V. Pyridopyrimidines of Biological Interest

A number of deaza analogs of pteroic acid (**182**, $R_1 = R_2 = OH$) have been prepared and examined by Rydon *et al.*[80] as antagonists of folic acid in *Streptococcus faecalis* and *Lactobacillus casei*. Two of the pyrido[3,2-*d*]pyrimidines (**183**, R = OH or OEt, $R_2 = NH_2$) showed



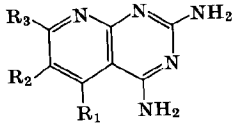
(182)



(183)

antifolic acid activity of the order of that of the known synthetic antagonist aminopterin,[139] and significant activity was also present in simpler 2,4-diaminopyrido[3,2-*d*]- and 2,4-diaminopyrido[2,3-*d*]-pyrimidines. No antitumor activity such as is shown by aminopterin[6,140] was found in any of these derivatives.[80]

G. H. Hitchings and his co-workers have made a comprehensive study[112,141] of antifolic acid activity in 2,4-diaminopyrimidines. They have demonstrated that very many such compounds, both simple and fused, show such activity. In the course of this work some pyrido[3,2-*d*]-pyrimidines and a large number of pyrido[2,3-*d*]pyrimidines[13,49,50,58,112,141] were shown to be highly active against a variety of pathogenic bacteria. Recent work has shown that 2,4-diamino 6-substituted or 5,6-disubstituted pyrido[2,3-*d*]pyrimidines (**184**) bearing hydrogen or a methyl group in the 5-position, and a substituent such as an alkyl group of five or six carbon atoms, or a benzyl group, in the 6-position



(**184**)

were potent inhibitors of bacterial dihydrofolate reductases and, thus, had general antibacterial activity. The action of such compounds was potentiated by sulfonamides and such a combination of drugs was active against both penicillin-resistant and penicillin-sensitive strains of *Staphylococcus aureus*.

Early reports[100,100a,142] of analgesic and antiarthritic activity in octahydropyrido[4,3-*d*]pyrimidines do not appear to have been substantiated, but a number of recent patents[90,95,95a,126] refer to the antipyretic, diuretic, bacteriostatic, sedative, and coronary-dilating activities of a series of 5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidines. Pharmacological properties claimed for 5,6-dihydropyrido[2,3-*d*]-pyrimidines[131] and pyrido[2,3-*d*]pyrimidine-2,4,5,7-tetraones[67] have not yet been confirmed.

139 E. Jacobsen, *in* "Biological Approaches to Cancer Chemotherapy" (R. V. C. Harris, ed.), p. 149. Academic Press, New York, 1961.

140 S. Farber, L. K. Diamond, R. D. Mercer, R. F. Sylvester, and J. A. Wolff, *New Engl. J. Med.* **238**, 787 (1948).

141 B. S. Hurlbert, R. Ferone, T. A. Herrmann, and G. H. Hitchings, M. Barnett, and S. R. M. Busby, *J. Med. Chem.* **11**, 711 (1968).

142 L. O. Randall and J. J. Selitto, *Arch. Intern Phamacodyn.* **111**, 409 (1957).

Cyclic Hydroxamic Acids

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I. Introduction

Although cyclic hydroxamic acids were made as early as 1881 by Friedländer and Ostermeier,[1,2,3] little attention was paid to this class

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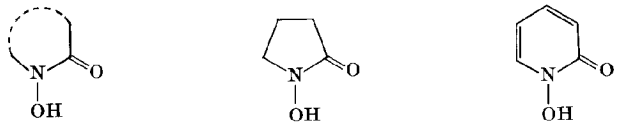
1 P. Friedländer and H. Ostermeier, *Ber. Deut. Chem. Ges.* **14**, 191 (1881).

2 P. Friedländer and H. Ostermeier, *Ber. Deut. Chem. Ges.* **15**, 332 (1882).

3 P. Friedländer, *Ber. Deut. Chem. Ges.* **47**, 3369 (1914).

of compounds until the characterization of the mold metabolite, aspergillic acid,[4] as a cyclic hydroxamic acid by Dutcher and Wintersteiner[5] in 1944. It is now recognized that cyclic and macrocyclic hydroxamic acids are widely distributed in nature and may occur as ferric complexes or as the free acids.

The structure of a cyclic hydroxamic acid can be generalized as **1**.



(1) **(2)** **(3)**

The name hydroxamic acid was first used by Lossen[6] in 1869, in the case of oxalohydroxamic acid, obtained from diethyl oxalate and hydroxylamine. Where this grouping forms part of the main cyclic system, however, the compound is named as a derivative of this system. In this review, **2** and **3** would be named as 1-hydroxy-2-pyrrolidone and 1-hydroxy-2-pyridone, respectively.

The following discussion of hydroxamic acids includes saturated systems, e.g., **2**, compounds such as **3**, derived from aromatic systems, *N*-hydroxyimides such as *N*-hydroxyglutarimide (**78**), and certain of their derivatives including thiohydroxamic acids. Naturally occurring cyclic hydroxamic acids are discussed to show the range of structural types that has been found, but macrocyclic polyhydroxamic acids are mentioned very briefly, because several comprehensive reviews of these compounds are already available.[7, 8, 9] The main purpose of this review is to summarize the methods available for the synthesis of cyclic hydroxamic acids, to outline their characteristic reactions, and to present some useful physical data. Their synthesis and some biological properties have previously been reviewed by Coutts.[9a]

[4] E. C. White and J. H. Hill, *J. Bacteriol.* **45**, 433 (1943).
[5] J. D. Dutcher and O. Wintersteiner, *J. Biol. Chem.* **155**, 359 (1944).
[6] H. Lossen, *Ann. Chem.* **150**, 314 (1869).
[7] O. Mikes and J. Turkova, *Chem. Listy* **58**, 65 (1964).
[8] W. Keller-Schierlein, V. Prelog, and H. Zähner, *Fortschr. Chem. Org. Naturstoffe* **22**, 279 (1964).
[9] J. B. Neilands, *Struct. Bonding (Berlin)* **1**, 59 (1966).
[9a] R. T. Coutts, *Can. J. Pharm. Sci.* **2**, 27 (1967).

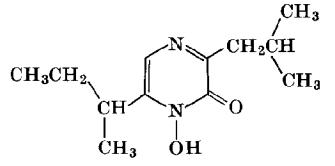
II. Naturally Occurring Compounds

Mikes and Turkova[7] have given a classification of naturally occurring hydroxamic acids in terms of their biological function or activity. They have distinguished: (*a*) growth factors, e.g., ferrichromes, mycobactin, and ferrioxamines, ferrichrysins, ferrirubins, etc.; (*b*) antibiotics, e.g., aspergillic acid, mycelianamide, albomycin, nocardamine; and (*c*) microbial pigments such as pulcherrimin.

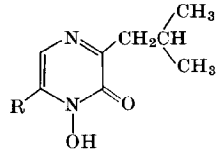
For the present purpose this is not a useful scheme and the naturally occurring compounds are arranged instead in order of increasing molecular complexity. Compounds that do not contain a cyclic hydroxamic acid structure are excluded.

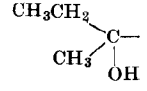
A. Aspergillic Acids

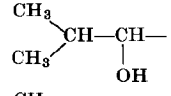
The first natural products shown to be cyclic hydroxamic acids belong to the group of aspergillic acids, formed by cultures of *Aspergillus flavus* and related organisms.

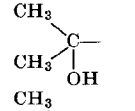


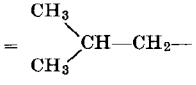
(4)



(5) R = 

(6) R = 

(7) R = 

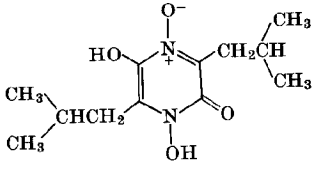
(8) R = 

Aspergillic acid (**4**),[4] hydroxy- (**5**),[10,11] neohydroxy- (**6**),[12] muta- (**7**),[13] and neo- (**8**)[14] aspergillic acids all show high antibacterial activity against gram-negative organisms.

The constitution of aspergillic acid was elucidated by Dutcher and Wintersteiner,[5,15] Newbold and Spring,[16] and Dunn *et al.*[17] It shows weakly acidic and basic properties, gives a wine-red color with ferric chloride, and is stable to hydrolysis with acid or alkali, a property in contrast to the behavior of aliphatic hydroxamic acids. Reduction of aspergillic acid with hydrazine gave deoxyaspergillic acid,[15] which was shown to be a 2-hydroxy-3,6-dialkylpyrazine. The nature of the alkyl groups was established by a synthesis[16] of racemic deoxy-aspergillic acid. Total syntheses of racemic aspergillic and neoaspergillic acid[18] and of mutaaspergillic acid[19] have recently been disclosed.

B. Pulcherrimin and Pulcherriminic Acid

Pulcherrimin, the red pigment from *Candida pulcherrima*, is a polymeric ferric complex[20] of pulcherriminic acid (**9**). The structure of

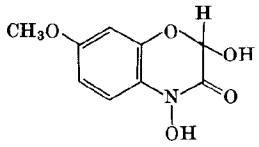


(**9**)

[10] A. E. O. Menzel, O. Wintersteiner, and G. Rake, *J. Bacteriol.* **46**, 109 (1943).
[11] J. D. Dutcher, *J. Biol. Chem.* **232**, 785 (1958).
[12] U. Weiss, F. Strelitz, H. Flow, and I. N. Asheshov, *Arch. Biochem. Biophys.* **74**, 150 (1958).
[13] S. Nakamura, *Bull. Agr. Chem. Soc. Japan* **23**, 65 (1959); **24**, 629 (1960); *Agr. Biol. Chem. (Tokyo)* **25**, 74, 658 (1961).
[14] R. G. Micetich and J. C. MacDonald, *J. Chem. Soc.* p. 1507 (1964).
[15] J. D. Dutcher, *J. Biol. Chem.* **171**, 321, 341 (1947).
[16] G. T. Newbold and F. S. Spring, *J. Chem. Soc.* p. 1864 (1948).
[17] G. Dunn, J. J. Gallagher, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.* p. S126 (1949).
[18] M. Masaki, Y. Chigira, and M. Ohta, *J. Org. Chem.* **31**, 4143 (1966).
[19] M. Sugiyama, M. Masaki, and M. Ohta, *Tetrahedron Letters* p. 845 (1967).
[20] A. J. Kluyver, J. P. Van der Walt, and A. J. Van Triet, *Proc. Natl. Acad. Sci. U.S.* **39**, 583 (1953).

pulcherriminic acid was clarified by MacDonald[21] and confirmed by a synthesis due to Ohta[22].

C. 2,4-Dihydroxy-7-methoxy-1,4-benzoxazin-3-one



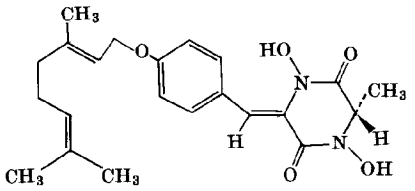
(**10**)

This cyclic hydroxamic acid (**10**)[23] and the related demethoxy compound have been isolated from corn seedlings. Both compounds are fungistatic agents.

D. Mycelianamide

The mold metabolite mycelianamide, isolated from the mycelium of strains of *Penicillium griseofulvum* Dierckx, was first investigated by Oxford and Raistrick[24]. The reinterpretation and extension of this work by Birch *et al.*[25] and the revision by Bates *et al.*[26] of the structure first proposed for the terpenoid side-chain,[25] have led to the formulation of mycelianamide as **11**. This structure has been confirmed by further degradations[27,28] and by a synthesis of racemic deoxymycelianamide by Gallina and co-workers.[28] The ready decomposition of the heterocyclic ring by either acid or alkali is discussed later (Section IV,C).

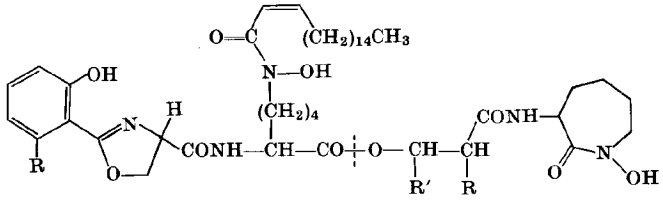
[21] J. C. MacDonald, *Can. J. Chem.* **41**, 165 (1963).
[22] A. Ohta, *Chem. Pharm. Bull. (Tokyo)* **12**, 125 (1964).
[23] O. Wahlroos and A. I. Virtanen, *Acta Chem. Scand.* **13**, 1906 (1959).
[24] A. E. Oxford and H. Raistrick, *Biochem. J.* **42**, 323 (1948).
[25] A. J. Birch, R. A. Massy-Westropp, and R. W. Rickards, *J. Chem. Soc.* p. 3717 (1956).
[26] R. B. Bates, J. H. Schauble, and M. Souček, *Tetrahedron Letters* p. 1683 (1963).
[27] C. Gallina, A. Romeo, G. Tarzia, and V. Tortorella, *Gazz. Chim. Ital.* **94**, 1301 (1964).
[28] C. Gallina, A. Romeo, V. Tortorella, and G. D'Agnelo, *Chem. Ind. (London)* p. 1300 (1966).



(11)

E. Mycobactins

Francis *et al.*[29] and Snow[30] have isolated from *Mycobacterium phlei* and *M. tuberculosis* two series of growth factors for *M. johnei*, containing the mycobactins P (**12**) and T (**13**), respectively.



(**12**) R = CH_3, R′ = CH_3CH_2

(**13**) R = H, R′ = CH_3

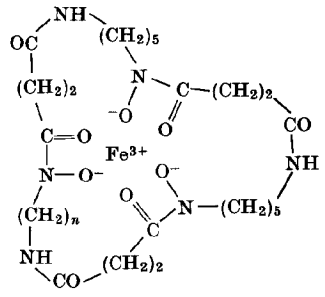
Mild alkaline hydrolysis cleaved the molecules as shown by the dotted line to give the carboxylic cobactic acids and the neutral cobactins. Acidic hydrolysis resulted in complex fission of the molecule into smaller fragments. No synthetic work in the mycobactin series has been reported, but the structures are based on very extensive degradations.

F. Nocardamine and Ferrioxamine E

The ferrioxamines[8, 9] form a large group of ferric trihydroxamates composed of residues of acetic acid, succinic acid, 1-amino-5-hydroxylaminopentane, and 1-amino-4-hydroxylaminobutane. Of these, only ferrioxamines E (**14**) and D_2 (**15**) are formally cyclic hydroxamic acids.

[29] J. Francis, H. M. Macturk, S. Madinaveitia, and G. A. Snow, *Biochem. J.* **55**, 596 (1953).

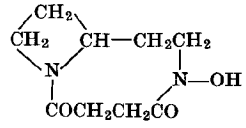
[30] G. A. Snow, *J. Chem. Soc.* p. 2588, 4080 (1954); *Biochem. J.* **81**, 4P (1961); **94**, 160 (1965); **97**, 166 (1965).



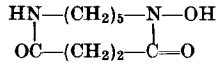
(**14**) $n = 5$

(**15**) $n = 4$

The iron-free ligand, deferrioxamine E, is identical[31] with nocardamine,[32] a metabolite from a *Nocardia* species, which was earlier erroneously formulated as **16**[33] and then **17**.[34]



(**16**)



(**17**)

III. Synthesis of Cyclic Hydroxamic Acids

Because of the great range of structures containing cyclic hydroxamic acid functions it is difficult to give a concise summary of the available synthetic methods. Nevertheless, the vast majority of published syntheses depend on condensation reactions involving only familiar processes of acylation or alkylation of hydroxylamine derivatives. The principles of such syntheses are outlined in a number of typical examples in Section III, A but no attempt has been made to cover all reported cases.

However, the oxidative processes and displacement reactions dealt with in Sections III, B and C are commonly used only in the synthesis

[31] W. Keller-Schierlein and V. Prelog, *Helv. Chim. Acta* **44**, 1981 (1961).

[32] A. Stoll, A. Brack, and J. Renz, *Schweiz. Z. Allgem. Pathol. Bakteriol.* **14**, 225 (1951).

[33] A. Stoll, J. Renz, and A. Brack, *Helv. Chim. Acta* **34**, 862 (1951).

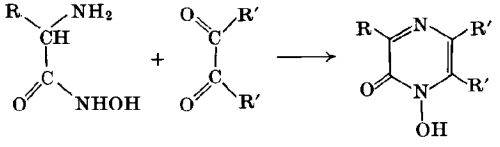
[34] R. F. C. Brown, G. Büchi, W. Keller-Schierlein, V. Prelog, and J. Renz, *Helv. Chim. Acta* **43**, 1868 (1960).

of cyclic hydroxamic acids. The formation of cyclic hydroxamic acids by reactions involving ring expansion is assigned a separate section (Section III, D) because the reaction sequences are frequently complex and deserving of detailed exposition, even though the final steps may involve standard condensation reactions.

A. Condensation Reactions

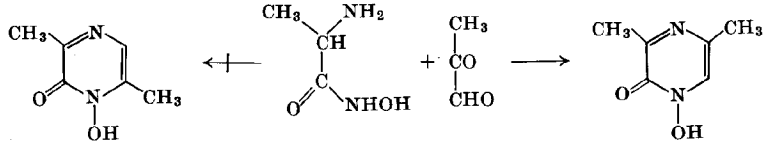
A variety of condensation processes can lead to cyclic hydroxamic acids. These involve either the condensation of two molecules or the intramolecular cyclization of a single compound. In some cases, a primary hydroxamic acid function is already present and formation of a cyclic compound can arise by suitable reaction on nitrogen. These processes will be dealt with first.

This type of synthesis has been used extensively in the preparation of hydroxamic acids resembling aspergillic acid. α-Aminohydroxamic acids react[35,36] with α-dicarbonyl compounds to yield pyrazine hydroxamic acids (**18**). Glyoxal and diacetyl react readily, but poor



(**18**)

yields are obtained with benzil. In the case of an unsymmetrical α-dicarbonyl reactant, the hydroxylamino nitrogen atom reacts with the more electrophilic carbonyl group. Condensation[35] of alanine hydroxamic acid with methyl glyoxal yielded **19** exclusively and not **20**. Because of this result, aspergillic acid analogs cannot be prepared

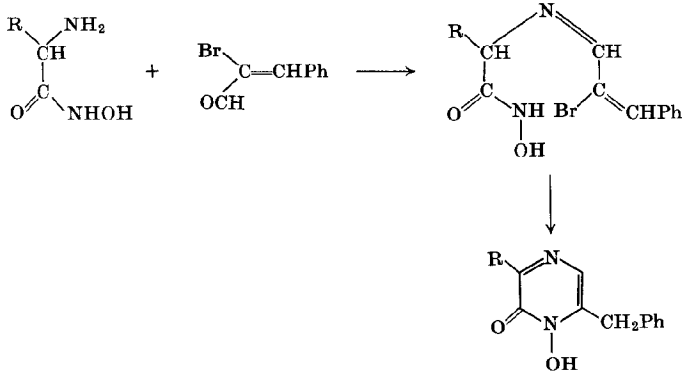


(**20**) (**19**)

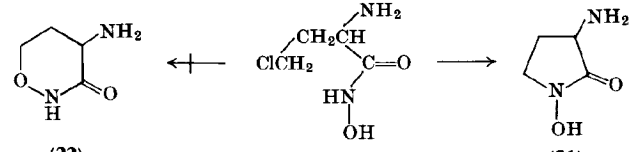
[35] G. Dunn, J. A. Elvidge, G. T. Newbold, W. C. Ramsay, F. S. Spring, and W. Sweeny, *J. Chem. Soc.* p. 2707 (1949).

[36] S. R. Safir and J. H. Williams, *J. Org. Chem.* **17**, 1298 (1952).

by this method. The aspergillic acid substitution pattern is obtained in the reaction of an α-aminohydroxamic acid with 2-bromocinnamaldehyde followed by base-catalyzed cyclization.

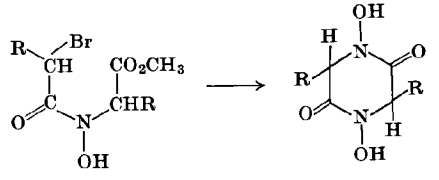


In a similar base-catalyzed cyclization, Smrt *et al.*[37] obtained a high yield of the pyrrolidone (**21**) from a γ-halogeno-α-aminobutyrohydroxamic acid, and were unable to isolate any of the six-membered ring compound (**22**).



(**22**) (**21**)

The *N*,*N*′-dihydroxydiketopiperazines (**24**) have been prepared by treatment[38] of the α-bromoacyl compounds (**23**) with excess of methanolic hydroxylamine.

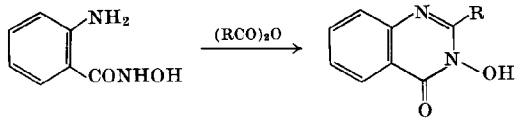


(**23**) (**24**)

[37] J. Smrt, J. Beranek, and M. Horak, *Collection Czech. Chem. Commun.* **24**, 1672 (1959).

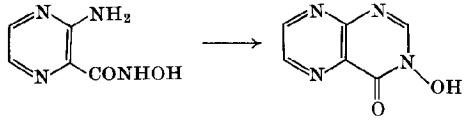
[38] A. H. Cook and C. A. Slater, *J. Chem. Soc.* p. 4130 (1956).

Quinazoline hydroxamic acids (**26**) can be prepared[39] by acylation of an *o*-aminobenzohydroxamic acid (**25**). An alternative procedure



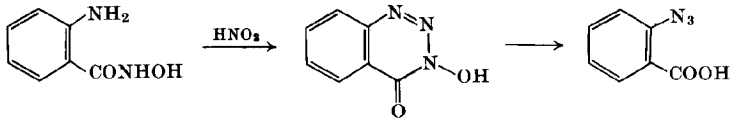
(**25**) (**26**)

involves reaction of an acylated amino acid with hydroxylamine. Amino acids derived from pyridine and pyrazine[40] have also been used in this reaction, the latter giving rise to a hydroxypteridone (**27**).



(**27**)

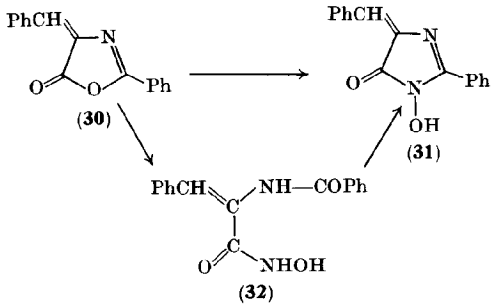
The action of nitrous acid on *o*-aminohydroxamic acids gave products that are believed[39] to be triazine hydroxamic acids, e.g., **28**. These gave a red color with ferric chloride, and **28** was converted by sodium hydroxide into *o*-azidobenzoic acid (**29**).



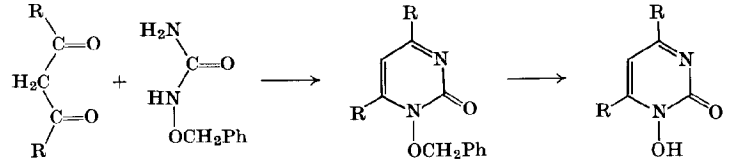
(**28**) (**29**)

Shaw and McDowell[41] have prepared imidazolone derivatives by cyclization of α-acylamino amides. In a variation of this reaction the azlactone (**30**) was gradually converted to the hydroxamic acid (**31**) by methanolic hydroxylamine. Sodium methoxide and hydroxylamine readily gave the acyclic hydroxamic acid (**32**) which could be cyclized to **31** by dilute acid. Benzyloxyurea has been used in the synthesis of pyrimidine hydroxamic acids (**33**) by reaction[42] with β-diketones followed by catalytic hydrogenation of the benzyl group. Protection

[39] D. Harrison and A. C. B. Smith, *J. Chem. Soc.* p. 2157 (1960).
[40] W. B. Wright and J. M. Smith, *J. Am. Chem. Soc.* **77**, 3927 (1955).
[41] E. Shaw and J. McDowell, *J. Am. Chem. Soc.* **71**, 1691 (1949).
[42] W. A. Lott and E. Shaw, *J. Am. Chem. Soc.* **71**, 70 (1949).

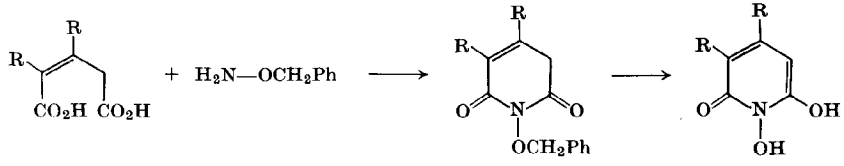


(**30**) (**31**) (**32**)



(**33**)

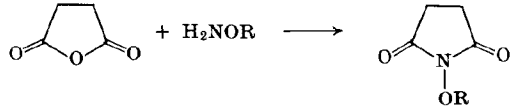
of a hydroxyl group played an important part in the preparation[43] of the 6-hydroxypyridones (**34**), in which benzyloxyamine was treated with a glutaconic acid. Ames and Grey[43] had previously been unable



(**34**)

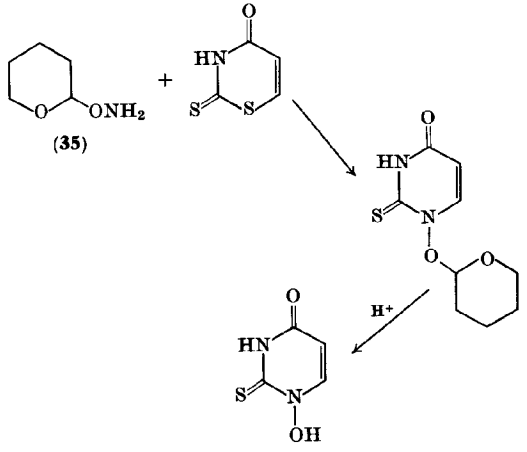
to demethylate a 2,6-dimethoxypyridine *N*-oxide and also could not oxidize 2,6-dibenzyloxypyridine to the *N*-oxide, presumably for steric reasons.

Other *N*-hydroxyimides have been obtained[43, 44] by reaction of benzyloxyamine with anhydrides, a process used many years ago[45] with hydroxylamine itself.



[43] D. E. Ames and T. F. Grey, *J. Chem. Soc.* p. 631 (1955).
[44] D. E. Ames and T. F. Grey, *J. Chem. Soc.* p. 3518 (1955).
[45] G. Errera, *Gazz. Chim. Ital.* **25** (2), 32 (1895).

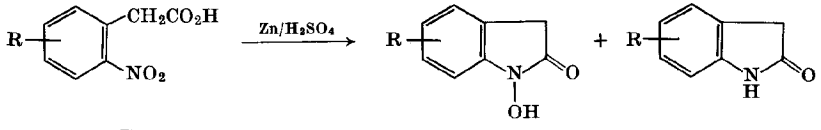
O-Tetrahydropyran-2-ylhydroxylamine (**35**)[46] shows considerable promise as a protected hydroxylamine for use in hydroxamic acid synthesis, as exemplified by the synthesis[46] of 1-hydroxy-2-thiouracil (**36**).



(**35**)

(**36**)

In general, a hydroxamic acid function results from the condensation of a hydroxylamine group with a carboxylic acid derivative. If these two groups are positioned suitably in the same molecule, spontaneous cyclization can occur. The most usual technique involves



(**37**) (**38**) (**39**)

reduction of a nitro ester to the hydroxylamine oxidation level and this can be achieved in several ways.

Wright and Collins[47] reduced *o*-nitrophenylacetic acids (**37**) with zinc and sulfuric acid and obtained a mixture of the hydroxamic acid (**38**) and lactam (**39**)

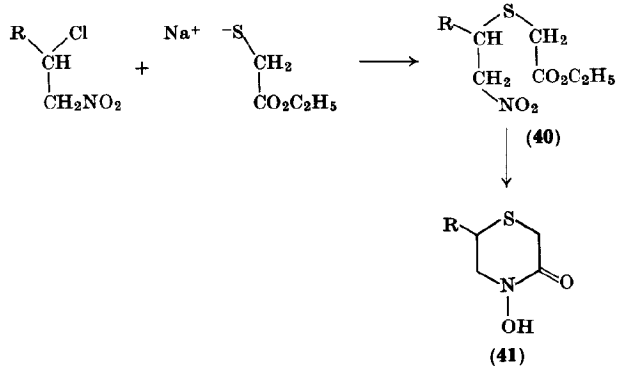
[46] R. N. Warrener and E. N. Cain, *Angew. Chem. Intern. Ed. English* **5**, 511 (1966).

[47] W. B. Wright and K. H. Collins, *J. Am. Chem. Soc.* **78**, 221 (1956).

Although the yields of **38** were high, the oxindole (**39**) was also formed as a by-product. This exemplifies the problem of reducing the nitro group specifically to a hydroxylamine.

Other zinc reductions have been used extensively. Zinc dust in aqueous ammonium chloride is a standard reagent for the reductive cyclization of nitro esters to hydroxamic acids. These reactions are usually carried out at low temperatures (0°–10°) to avoid further reduction. Despite the fact that good yields can often be obtained, these reductions are highly capricious, depending on the quality of the zinc (impurities seem to improve the reaction) and other unknown factors.

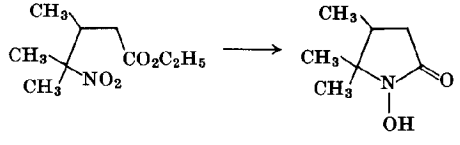
By this method, Chauveau and Mathis[48] have prepared cyclic hydroxamic acids (**41**) containing a sulfur atom in the ring. The acyclic precursors (**40**) were formed by alkylation of a thiol anion.



(**40**)

(**41**)

Earlier, the reduction of γ-nitro esters with zinc and ammonium chloride had been shown[49] to provide a suitable route to *N*-hydroxy 2-pyrrolidones, e.g., **42**. Various catalytic hydrogenation procedures can also effect the same reductive cyclization.[49, 50]



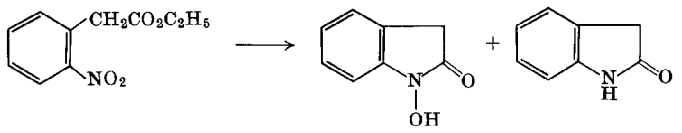
(**42**)

[48] A. Chauveau and F. Mathis, *Compt. Rend.* **261**, 481 (1965).

[49] R. Bonnett, V. M. Clark, and Sir A. Todd, *J. Chem. Soc.* p. 2102 (1959).

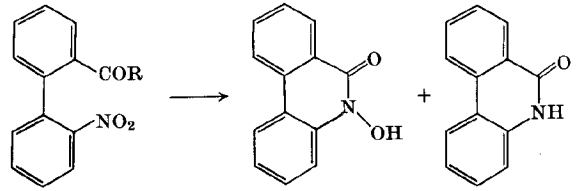
[50] B. Reichert and E. Wegner, *Ber. Deut. Chem. Ges.* **71**, 1254 (1938).

In the catalytic hydrogenation of ethyl 2-nitrophenyl acetate (**43**), Di Carlo[51] observed a small amount of the cyclic hydroxamic acid (**44**) in addition to the expected lactam (**45**). Following this result, a



(**43**) (**44**) (**45**)

thorough study of the platinum oxide-catalyzed hydrogenation of 2-nitro-2′-carboxybiphenyl (**46**, R = OH) and some of its derivatives (**46**, R = OMe, NH_2, ONa) has been carried out.[52] In general, both



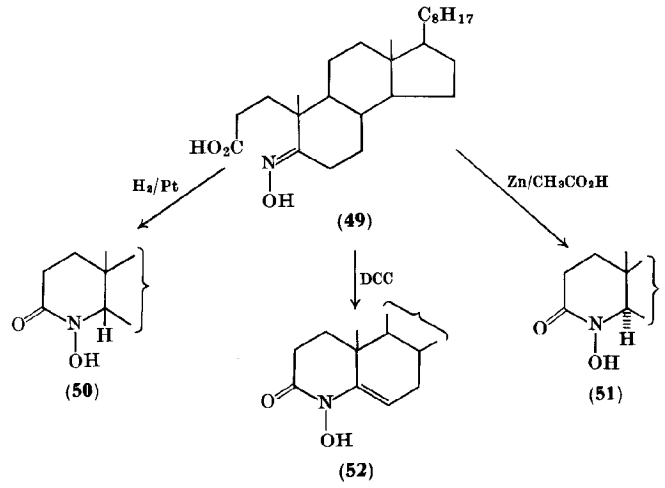
(**46**) (**47**) (**48**)

products (**47** and **48**) corresponding to reduction of the nitro group to a hydroxylamine or amine are formed.

In all cases, a higher percentage of hydroxylamino trapping occurs in the presence of mineral acid, and the hydroxylamino trapping abilities of the carboxy derivatives increase as R = OH < OMe < NH_2. This order is reversed in the absence of mineral acid. Presumably the carboxyl derivative is protonated in the presence of acid and thus becomes a better electrophile.

An interesting comparison between a catalytic hydrogenation and a zinc and acetic acid reduction is observed[53] in the case of the oximino acid (**49**). The *cis*-fused hydroxamic acid (**50**) was the sole

[51] F. J. Di Carlo, *J. Am. Chem. Soc.* **66**, 1420 (1944).
[52] C. W. Muth, J. R. Elkins, M. L. DeMatte, and S. T. Chiang, *J. Org. Chem.* **32**, 1106 (1967).
[53] J. T. Edward and P. F. Morand, *Can. J. Chem.* **38**, 1317 (1960).

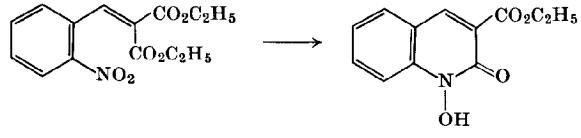


(**50**) (**49**) (**52**) (**51**)

product of catalytic reduction, whereas zinc and acetic acid gave the *trans*-fused structure (**51**).

The same oximino acid (**49**) underwent[54] a cyclodehydration on treatment with dicyclohexyl carbodiimide to form the unsaturated hydroxamic acid (**52**) in almost quantitative yield.

Perhaps the most reliable method for the reductive cyclization of a nitro ester to a hydroxamic acid is that which involves treatment with sodium borohydride in the presence of palladium on charcoal.[55] Although under these conditions aromatic nitro compounds are reduced to amines, *o*-nitro esters such as **53**, in which the ester group is suitably oriented with respect to the nitro group, give good yields[56, 57] of cyclic hydroxamic acids (**54**). Coutts and his co-



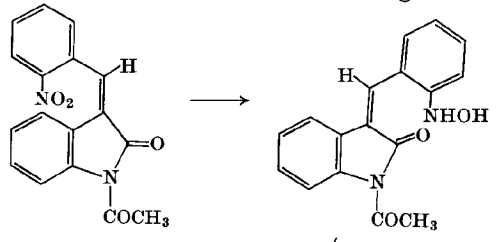
(**53**) (**54**)

[54] N. J. Doorenbos and M. T. Wu, *Chem. Ind.* (*London*) p. 648 (1965).
[55] T. Neilson, H. C. S. Wood, and A. G. Wylie, *J. Chem. Soc.* p. 371 (1962).
[56] R. T. Coutts and D. G. Wibberley, *J. Chem. Soc.* p. 4610 (1963).
[57] D. Noble and D. G. Wibberley, *J. Med. Chem.* **9**, 974 (1966).

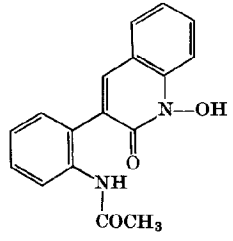
workers[58, 59] have found this method useful for a variety of cyclic hydroxamic acids with oxygen and sulfur heteroatoms in the ring.

In one particular example, an interesting intramolecular acylation occurred.[60] Reduction of *cis*-*N*-acetyl-*o*-nitrobenzylideneoxindole (**55**) gave rise to a cyclic hydroxamic acid, assigned structure **56**.

The proposed reaction pathway involves reduction and rotation to the *trans*-isomer followed by an intramolecular cyclization and displacement of an acetamide group. It is significant that the *N*-acetyl group is required and that an amino group is presumably not a good enough leaving group to allow this bond cleavage.



(55)



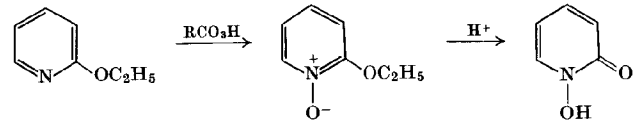
(56)

B. Oxidative Processes

Because of their higher oxidation level with respect to both amides and nitrones, hydroxamic acids have been sought from either by oxidative processes.

[58] R. T. Coutts and K. W. Hindmarsh, *Can. J. Pharm. Sci.* **1**, 11 (1966).
[59] R. T. Coutts and E. M. Smith, *Can. J. Chem.* **45**, 975 (1967).
[60] R. A. Abramovitch, R. T. Coutts, and N. J. Pound, *Chem. Ind. (London)* p. 1871 (1967).

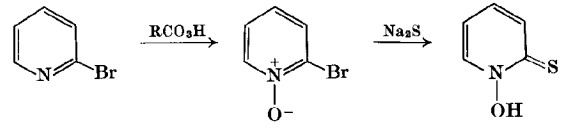
In the early drive to prepare analogs of aspergillic acid, Newbold, Spring, and their collaborators[16, 61, 62] established the peracid oxidation of 2-oxygenated pyridines (**57**) as a generally useful hydroxamic acid synthesis. The 2-hydroxy group is usually etherified, thus requiring acid hydrolysis[63] as in the sequence (**57** → **59**), or hydrogenolysis



(57) (58) (59)

in the case of a benzyloxy group.[64] A wide variety[65, 66] of ring nitrogen atoms have been oxidized in this way, but steric factors are often critical.[43]

In a variation of this method, 2-bromopyridine *N*-oxide (**60**) has been converted[67] by sodium sulfide to the thiohydroxamic acid (**61**).



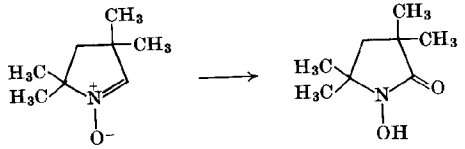
(60) (61)

2-Fluoro and 3- or 5-nitro-2-chloropyridine *N*-oxides may be converted[68, 69] to the corresponding 1-benzoyloxy-2-pyridones by reaction with benzoic acid alone.

In alicyclic systems, more emphasis has been placed on oxidation of nitrones. At least one aldonitrone of the pyrroline series (**62**) undergoes autoxidation[70] to the hydroxamic acid (**63**). This is probably a

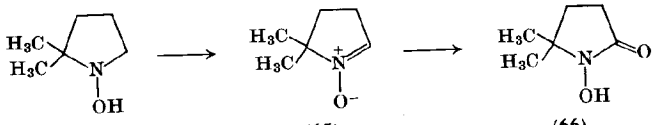
[61] K. G. Cunningham, G. T. Newbold, F. S. Spring, and J. Stark, *J. Chem. Soc.* p. 2091 (1949).
[62] G. T. Newbold and F. S. Spring, *J. Chem. Soc.* p. S133 (1949).
[63] L. A. Paquette, *Tetrahedron* **22**, 25 (1966).
[64] E. Shaw, *J. Am. Chem. Soc.* **71**, 67 (1949).
[65] M. Colonna and C. Runti, *Gazz. Chim. Ital.* **82**, 513 (1952).
[66] H. Yamanaka, *Chem. Pharm. Bull. (Tokyo)* **7**, 141 (1959).
[67] E. Shaw, J. Bernstein, K. Losee, and W. A. Lott, *J. Am. Chem. Soc.* **72**, 4362 (1950).
[68] D. Sarantakis, J. K. Sutherland, C. Tortorella, and V. Tortorella, *Chem. Commun.* p. 105 (1966).
[69] V. Tortorella, *Chem. Commun.* p. 308 (1966).
[70] D. St. C. Black, Ph.D. Thesis, Univ. of Cambridge, 1963.

free-radical process similar to the autoxidation of an aldehyde to a carboxylic acid, but this has not been established. However, in



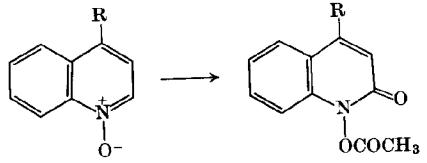
(62) (63)

general,[71] an aldonitrone can be oxidized rapidly to its related hydroxamic acid by ferric chloride. This reagent is also capable of oxidizing a hydroxylamine, through a nitrone, to a hydroxamic acid (e.g., **64** → **66**).



(64) (65) (66)

Ochiai and Ohta[72] have used lead tetraacetate in benzene to convert aromatic *N*-oxides (**67**) to the corresponding acetylated hydroxamic acids (**68**). Similar oxidation[73] of quinoline and isoquinoline *N*-oxides



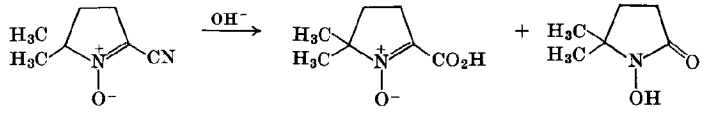
(67) (68)

to the corresponding *N*-hydroxycarbostyrils can be effected by alkaline ferricyanide.

[71] J. F. Elsworth and M. Lamchen, *J. Chem. Soc.* C, 1477 (1966).
[72] E. Ochiai and A. Ohta, *Chem. Pharm. Bull.* (*Tokyo*) **10**, 1260 (1962).
[73] M. Hamana and M. Yamazaki, *Chem. Pharm. Bull.* (*Tokyo*) **10**, 51 (1962).

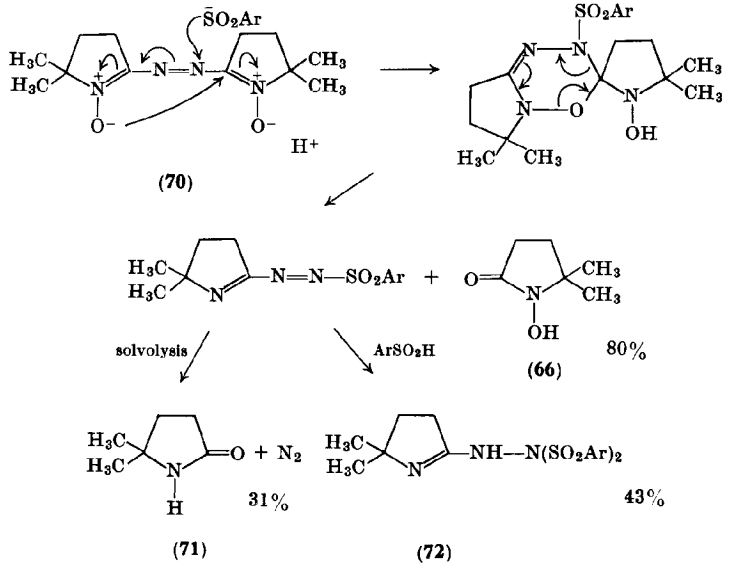
C. Displacement Reactions

Bonnett *et al.*[74] observed the formation of the pyrrolidone hydroxamic acid (**66**) as a by-product in the alkaline hydrolysis of a 2-cyanonitrone (**69**). This displacement of cyanide by hydroxyl seems to be quite general.



(69) (66)

During a study of azonitrones (**70**), Forrester and Thomson[75] showed that reaction with toluene-*p*-sulfinic acid resulted in nitrogen evolution and formation of the hydroxamic acid (**66**) together with the pyrrolidone (**71**) and the amidine (**72**). These workers suggested the following reaction course. Although the yield of hydroxamic acid was high, the method is not likely to be of preparative value.



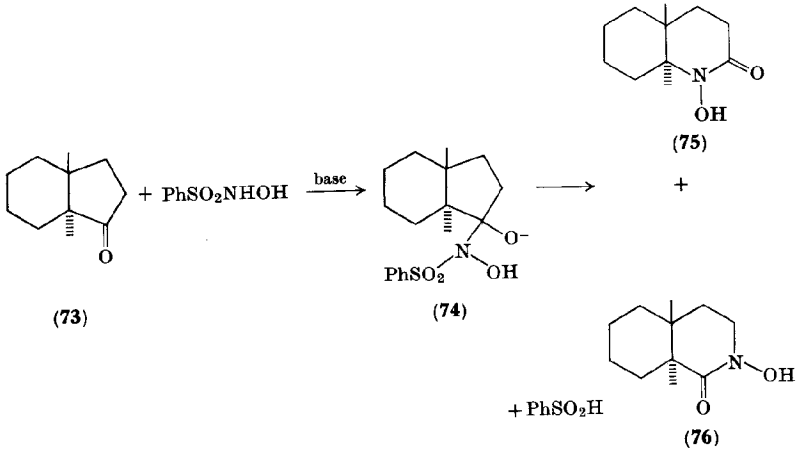
(70) (66) (71) (72)

[74] R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and Sir A. Todd, *J. Chem. Soc.* p. 2099 (1959).
[75] A. R. Forrester and R. H. Thomson, *J. Chem. Soc.* C, 382 (1966).

D. Ring Expansions

Several reactions are particularly applicable to the synthesis of cyclic hydroxamic acids as they involve some kind of ring expansion. Some are quite general reactions which are of high preparative utility, whereas others exist as fairly isolated examples which have not as yet been generalized.

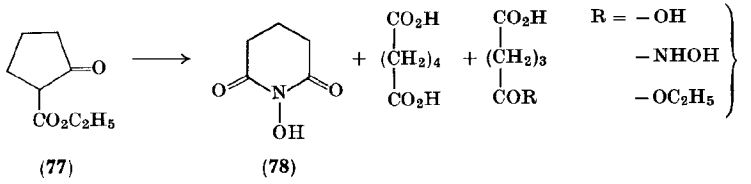
The method which has been of most preparative value is that established by Panizzi *et al.*[76] and Di Maio and Tardella.[77] Benzenesulfonhydroxamic acid (**74**), known as Piloty's acid, reacts with a cyclic ketone (**73**) in alkaline media at 0°, to produce the ring-expanded hydroxamic acids (**75** and **76**) in approximately equal yield.



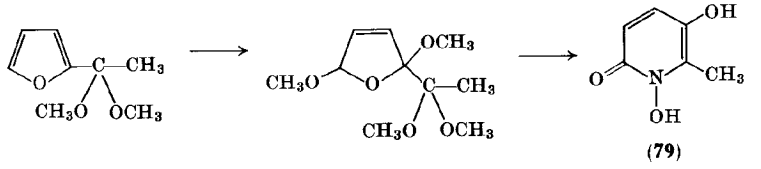
The reaction is based on an early observation by Angeli and Ahrens[78] that Piloty's acid converted aldehydes to hydroxamic acids, and this has formed the basis of the Angeli–Rimini aldehyde test.[79] Di Maio and Tardella[80] propose the above reaction sequence, consistent with the observed second-order kinetics. The possibility that benzenesulfonhydroxamic acid would decompose in alkali to give nitroxyl (HNO)

[76] L. Panizzi, G. Di Maio, P. A. Tardella, and L. d'Abbiero, *Ricerca Sci. Suppl* **31**, 312 (1961).
[77] G. Di Maio and P. A. Tardella, *Gazz. Chim. Ital.* **91**, 1124 (1961).
[78] A. Angeli and A. Ahrens, *Samml. Chem. Tech. Vortrage* **13**, 2 (1908).
[79] N. D. Cheronis and J. B. Entrikin, "Semimicro Qualitative Organic Analysis," p. 123. Crowell, New York, 1947.
[80] G. Di Maio and P. A. Tardella, *Gazz. Chim. Ital.* **96**, 526 (1966).

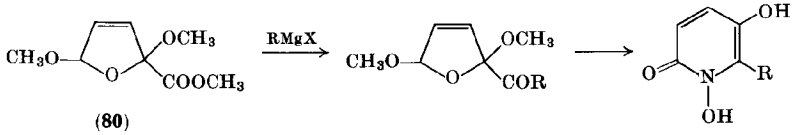
and the benzenesulfinate anion was rejected by these workers, because initial addition of sodium benzenesulfinate does not affect the reaction rate. The related conversion of a reactive halide to an oxime by Piloty's acid has also been shown[81] not to involve nitroxyl. Di Maio and d'Abbiero[82] also report that Piloty's acid reacted with 2-carbethoxycyclopentanone (**77**) to yield *N*-hydroxyglutarimide (**78**), glutaric acid, its half hydroxamic acid, and its half-ethyl ester, and adipic acid.



The overall conversion[83] of a 2-furyl ketal to a 6-substituted 1-hydroxy-2-pyridone (**79**) can be effected by electrolysis in methanol followed by reaction with hydroxylamine. A Grignard reagent can



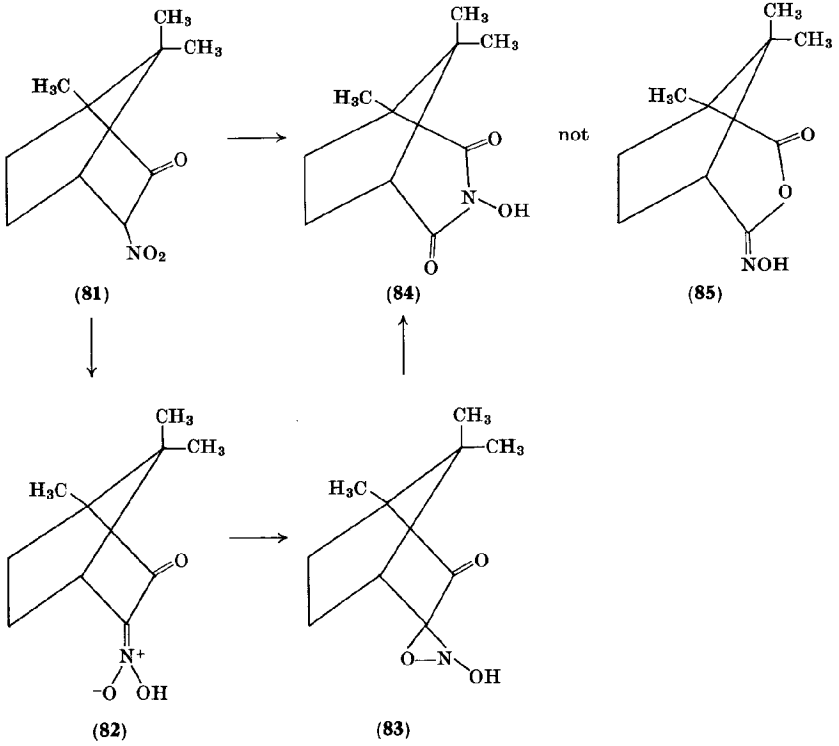
introduce a variety of 6-substituents into the 1-hydroxypyridone via a furan 2-carboxylic ester which gives **80** on electrolysis in methanol.



The literature contains several examples of the rearrangement of a nitro group to a hydroxamic acid function. In two cases an adjacent carbonyl group is present, so that the rearrangement products are *N*-hydroxyimides.

[81] P. A. S. Smith and G. E. Hein, *J. Am. Chem. Soc.* **82**, 5731 (1960).
[82] G. Di Maio and L. d'Abbiero, *Gazz. Chim. Ital.* **93**, 191 (1963).
[83] J. T. Nielsen, N. Elming, and N. Clauson-Kaas, *Acta Chem. Scand.* **9**, 30 (1955).

In 1898, Lowry[84] observed that α-nitrocamphor (**81**) under Nef conditions did not give the expected α-diketone, but instead a compound to which he assigned, with little evidence, the oximino anhydride structure (**85**). This structure was recently corrected by Larson and Wat[85] to the *N*-hydroxyimide (**84**).



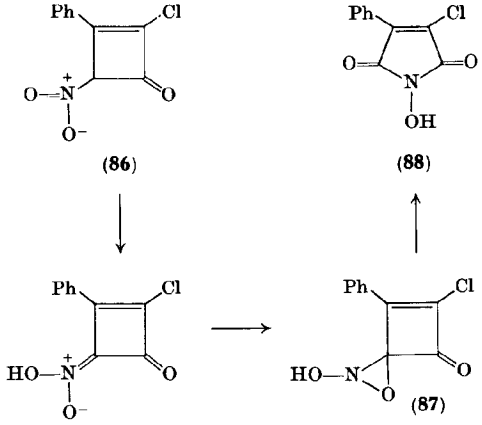
(**81**) (**84**) (**85**)

(**82**) (**83**)

The sequence (**81** → **84**) has been proposed[85,86] to account for this process which involves decomposition of the *aci*-nitro anion by strong acid. The α-carbonyl group presumably stabilizes the *aci*-salt and thus could be responsible for inhibiting the normal Nef reaction. A similar transformation has been observed[87] in the case of a 16-nitro-17-oxo steroid.

[84] T. M. Lowry, *J. Chem. Soc.* p. 986 (1898).
[85] H. O. Larson and E. K. W. Wat, *J. Am. Chem. Soc.* **85**, 827 (1963).
[86] D. St. C. Black, *J. Chem. Educ.* Submitted for publication (1968).
[87] A. Hassner and J. Larkin, *J. Am. Chem. Soc.* **85**, 2181 (1963).

Breslow and co-workers[88] discovered the thermal ring expansion of the nitrobutenone (**86**) to the *N*-hydroxymaleimide (**88**) which may be mechanistically similar to the abnormal Nef reaction of α-nitrocamphor. Breslow postulated the *N*-hydroxyoxaziran intermediate



(**86**) (**88**)

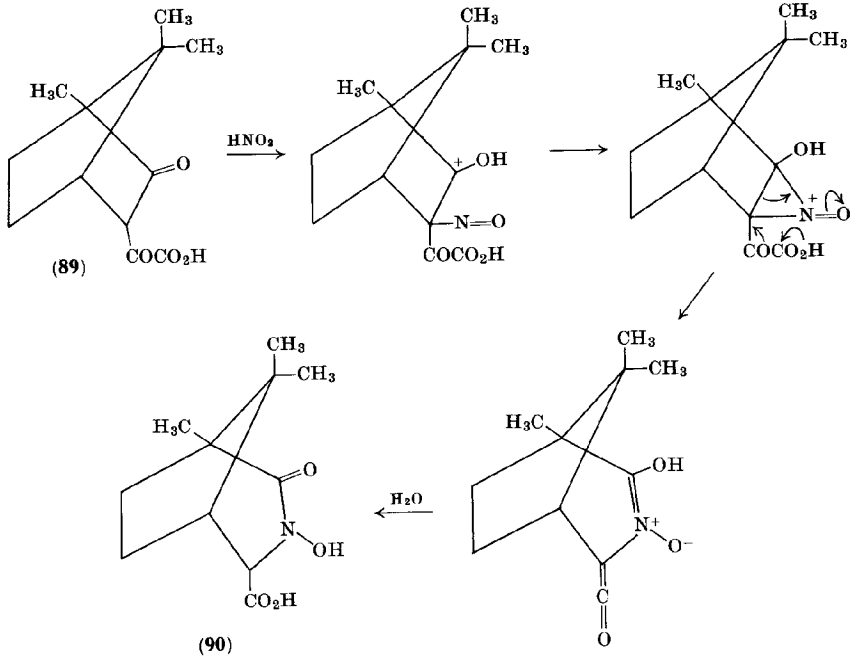
(**87**)

(**87**), but suggested that acyl migration to oxygen would form the oximinoanhydride, which could then be converted to the product. Such oxaziran decomposition would give rise to the Lowry structure in the case of α-nitrocamphor, and it seems more reasonable to postulate acyl migration to nitrogen, a process which would directly give the *N*-hydroxyimide (**88**). This proposal is consistent with the known rearrangements[89,90] of oxaziranes.

It is possible that these rearrangements are quite general, but so far, this generality has not been established.

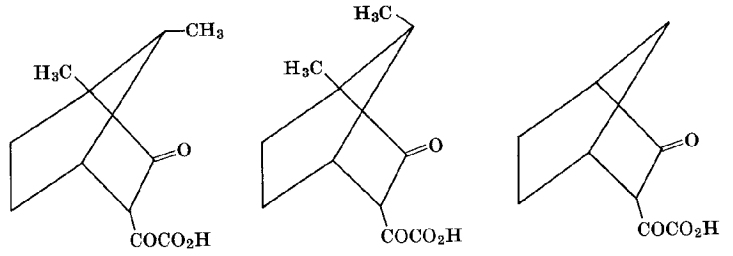
In a study of the nitrosation of camphor-3-glyoxylic acid (**89**), Chorley and Lapworth[91] isolated a compound whose structure (**90**) has recently been clarified by Hatfield and Huntsman.[92] Decarboxylation and ring expansion occur and the reaction is rationalized in the sequence **89** → **90**. The buttressing effect of a methyl group on

[88] R. Breslow, D. Kivelevich, M. J. Mitchell, W. Fabian, and K. Wendel, *J. Am. Chem. Soc.* **87**, 5132 (1965).
[89] W. D. Emmons, *in* "Heterocyclic Compounds with Three- and Four-membered Rings" (A. Weissberger, ed.), Pt. I, p. 624. Wiley (Interscience), New York, 1964.
[90] E. Schmitz, *Advan. Heterocyclic Chem.* **2**, 85 (1963).
[91] P. Chorley and A. Lapworth, *J. Chem. Soc.* **117**, 728 (1920).
[92] L. D. Hatfield and W. D. Huntsman, *J. Org. Chem.* **32**, 1800 (1967).



(89) (90)

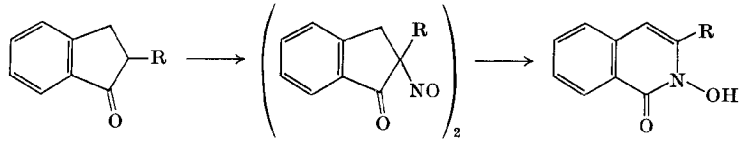
the endomethylene bridge appears to be important, as β-santenone-3-glyoxylic acid (**91**) behaved similarly, whereas the α-isomer (**92**) and norcamphor-3-glyoxylic acid (**93**) did not yield hydroxamic acids. A similar kind of rearrangement occurs[93] during nitrosation of



(91) (92) (93)

[93] E. J. Moriconi, F. J. Creegan, C. K. Donovan, and F. A. Spano, *J. Org. Chem.* **28**, 2215 (1963).

2-alkyl-1-indanones (**94**) and the corresponding hydroxyisocarbostyrils (**95**) are obtained. Moriconi and Creegan[94] have studied this



(94) (95)

conversion extensively because of its synthetic utility. It is noteworthy that the Beckmann rearrangement of 1-indanone oxime[95] and the Schmidt reaction on 1-indanone[96] lead predominantly to the aryl migration product, 3,4-dihydrocarbostyril (**96**). In general, *t*-butyl

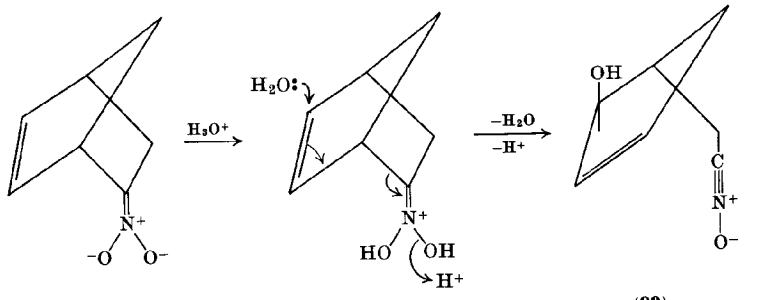
(96) (97)

nitrite was used for the nitrosation of indanones and the rearrangement was found to occur in both acidic and basic conditions. Moriconi and Creegan proposed mechanistic sequences involving ring cleavage followed by recyclization of an oximinocarboxylic acid derivative such as **97**.

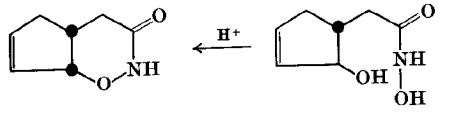
A further type of nitro-group rearrangement gives rise to a cyclic hydroxamic ether. Noland *et al.*[97] describe the action of cold, dilute sulfuric acid on the sodium salt of 5-nitronorbornene (**98**), which results in conversion to the oxazinone (**101**). This complex rearrangement is rationalized by the sequence **98** → **101** involving intermediate formation of the nitrile oxide (**99**) and the hydroxamic acid (**100**).

Robinson and co-workers[98, 99] have studied the photorearrangement of steroidal 17-nitrites (**102**) to cyclic hydroxamic acids (**103**) in good

[94] E. J. Moriconi and F. J. Creegan, *J. Org. Chem.* **31**, 2090 (1966).
[95] F. S. Kipping, *J. Chem. Soc.* **65**, 480 (1894).
[96] L. H. Briggs and G. C. De Ath, *J. Chem. Soc.* p. 456 (1937).
[97] W. E. Noland, J. H. Cooley, and P. A. McVeigh, *J. Am. Chem. Soc.* **81**, 1209 (1959).
[98] C. H. Robinson, O. Gnoj, A. Mitchell, R. Wayne, E. Townley, P. Kabasakalian, E. P. Oliveto, and D. H. R. Barton, *J. Am. Chem. Soc.* **83**, 1771 (1961).
[99] C. H. Robinson, O. Gnoj, A. Mitchell, E. P. Oliveto, and D. H. R. Barton, *Tetrahedron* **21**, 743 (1965).

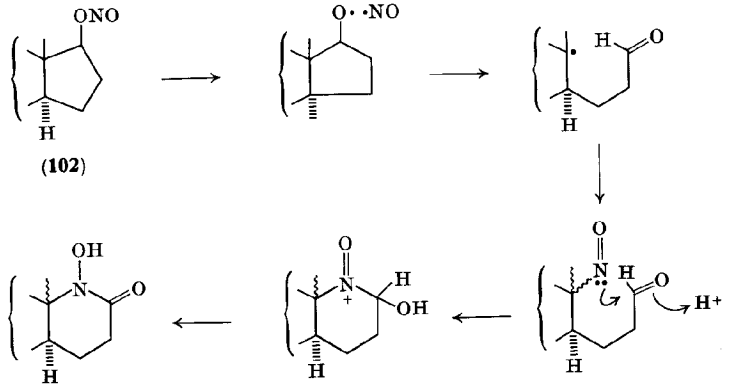


(98) (99)



(101) (100)

yield. The hydroxamic acid function is considered to arise via carbon–carbon fission of an intermediate alkoxy radical and this is supported by the isolation from the same photolysis reaction mixture of two isomeric hydroxamic acids, shown to be epimeric at C-13. The suggested pathway for this ring expansion is shown in sequence **102** → **103**. This formation of hydroxamic acids appears to be

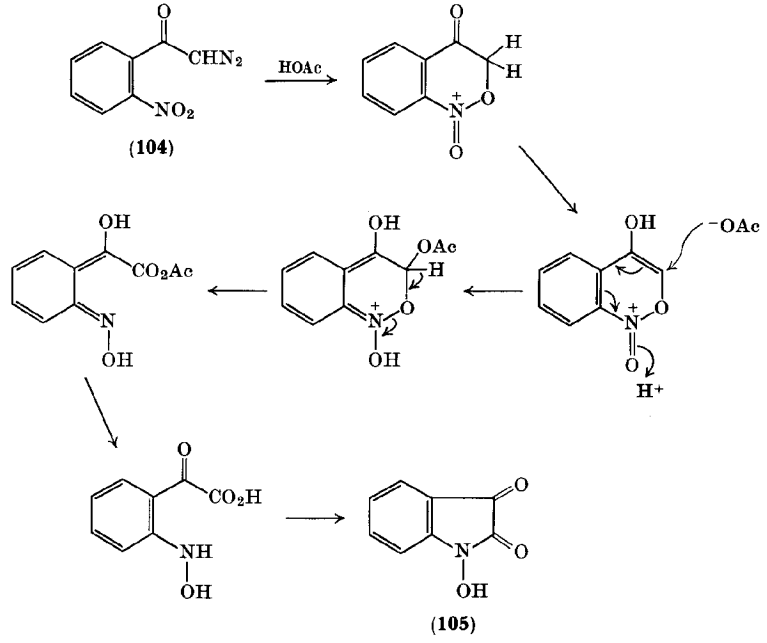


(102)

(103)

perfectly general, but its use has so far been confined to the steroid field.

Taylor and Eckroth[100] have recently investigated the mechanism of the acid-catalyzed conversion of *o*-nitrobenzoyldiazomethane (**104**) to *N*-hydroxyisatin (**105**), discovered by Arndt *et al.*[101] Labeling studies with ^{14}C in the diazo carbon atom gave results which ruled out a Wolff rearrangement, as all the label appeared in the isatin C-2 position. The following mechanistic pathway (**104** → **105**) is favored over an alternative one proposed earlier by Moore and Ahlstrom.[102]



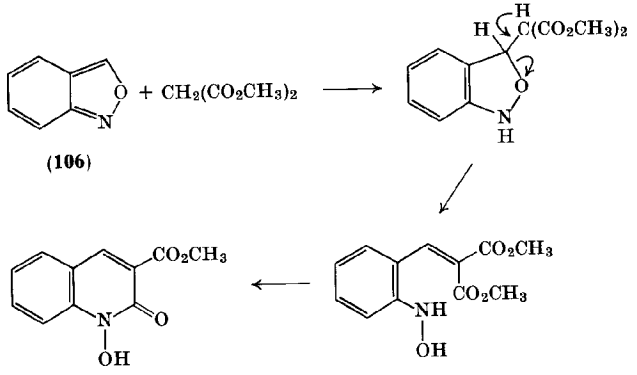
(104)

(105)

Taylor and Bartulin[103] have recently shown that anthranil (**106**) reacts with a variety of active methylene compounds to give quinoline

[100] E. C. Taylor and D. R. Eckroth, *Tetrahedron* **20**, 2059 (1964).
[101] F. Arndt, B. Eistert, and W. Partale, *Ber. Deut. Chem. Ges.* **60**, 1364 (1927).
[102] J. A. Moore and D. H. Ahlstrom, *J. Org. Chem.* **26**, 5254 (1961).
[103] E. C. Taylor and J. Bartulin, *Tetrahedron Letters* p. 2337 (1967).

1-oxides in almost quantitative yield. In the reaction with dimethyl malonate, the hydroxamic acid (**107**) is produced in 80% yield and the following mechanism (**106** → **107**) is proposed.



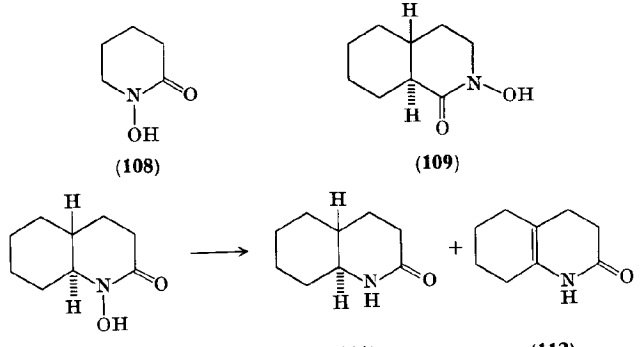
(**106**)

(**107**)

IV. Characteristic Reactions

A. Thermal Decomposition

When heated at or about their melting points cyclic hydroxamic acids commonly decompose to give the corresponding lactams. Thus,



(**108**) (**109**)

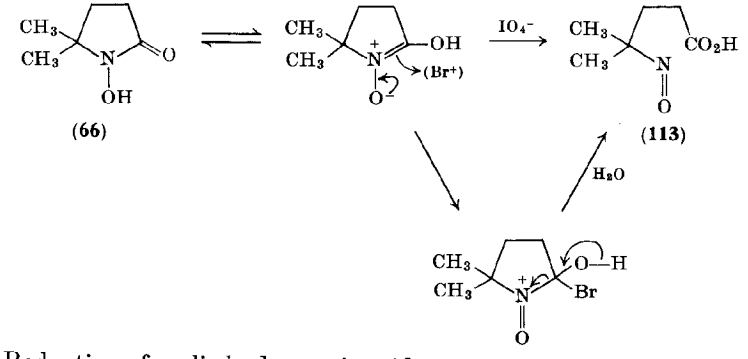
(**110**) (**111**) (**112**)

(**96**)

aspergillic acid (**4**) when heated with a little copper chromite over a free flame gave 32% deoxyaspergillic acid.[15] A similar decomposition has been observed with 1-hydroxyuracil.[104] The thermal decomposition of alicyclic hydroxamic acids during 2–4 hours at 220°–240° *in vacuo* has been investigated by Di Maio and Tardella.[105] Compounds **108**, **109**, and **110** gave the corresponding lactams by loss of oxygen, but particularly in the bicyclic series unsaturated and aromatic lactams were also formed, e.g., **110** → **111**, **112**, and **96**.

B. Oxidation and Reduction

Alicyclic hydroxamic acids undergo several specific oxidative cleavage reactions which may be of diagnostic or preparative value. In the pyrrolidine series compounds of type **66** have been oxidized with sodium hypobromite[70] or with periodates[106] to give γ-nitroso acids (**113**). Ozonolysis gives the corresponding γ-nitro acids.[70] The related cyclic aldonitrones are also oxidized by periodate to nitroso acids, presumably via the hydroxamic acids.[107] This periodate fission was used[108] in the complex degradation of Δ^{16}-nitrones derived from aconitine.

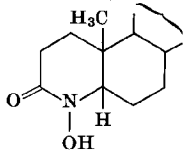


(**66**) (**113**)

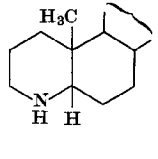
Reduction of cyclic hydroxamic acids generally leads to lactams or the corresponding amines. Chemical methods have frequently been preferred to catalytic hydrogenation, probably because the choice of

[104] W. Klötzer, *Monatsh. Chem.* **95**, 1729 (1964).
[105] G. Di Maio and P. A. Tardella, *Gazz. Chim. Ital.* **94**, 590 (1964).
[106] V. M. Clark, B. Sklarz, and Sir A. Todd, *J. Chem. Soc.* p. 2123 (1959).
[107] A. K. Qureshi and B. Sklarz, *J. Chem. Soc.* **C**, 412 (1966).
[108] F. W. Bachelor, R. F. C. Brown, and G. Büchi, *Tetrahedron Letters* p. 1 (1960).

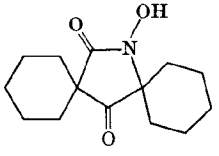
catalyst for the latter is critical. Thus, 1-hydroxy-2-pyridone was inert to palladium catalysts,[42, 109] but hydrogenolysis to 2-pyridone occurred readily over Raney nickel in methanol.[109] 1-Hydroxy-2-pyridone also resisted the action of stannous chloride or ammonium sulfide,[42] and chemical reduction of similar aromatic hydroxamic acids may require more powerful reagents such as red phosphorus and hydriodic acid,[42] sodium dithionite in hot aqueous ethanol,[39, 110] or hydrazine.[35] Reduction of aspergillic acid (**4**) to deoxyaspergillic acid has been achieved by pyrolytic deoxygenation, by heating with red phosphorus and hydriodic acid in acetic acid, and by heating with



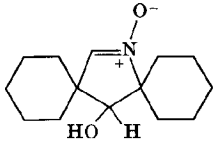
(**114**)



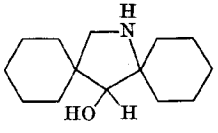
(**115**)



(**116**)



(**117**)



(**118**)

hydrazine at 100°, but not by hydrogenation.[15] Vigorous reduction of the steroidal hydroxamic acid (**114**) with tin and ethanolic hydrochloric acid gave[53] the corresponding amine (**115**), but milder combinations, particularly zinc and acetic acid, generally give lactams.[99, 25] Reduction with hydrazine in ethylene glycol under reflux has been used[99] to give ring D lactams in steroidal systems. The scope of hydride reductions has not been very fully explored; 4-hydroxy-4-aza-5-α-cholestan-3-one with $LiAlH_4$ in boiling ether for 12 hours

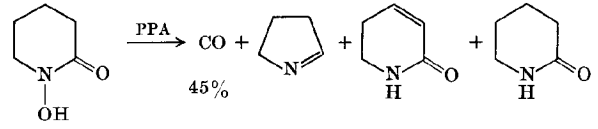
[109] E. Hayashi, H. Yamanaka, and T. Higashino, *Chem. Pharm. Bull. (Tokyo)* **7**, 149 (1959).

[110] G. T. Newbold, W. Sharp, and F. S. Spring, *J. Chem. Soc.* p. 2679 (1951).

gave[53] the amine, 4-aza-5-α-cholestane, but similar reduction[111] of the spiro compound (**116**) with $LiAlH_4$ gave the aldonitrone (**117**). In the latter case extended treatment with $LiAlH_4$ in tetrahydrofuran gave the amine (**118**).

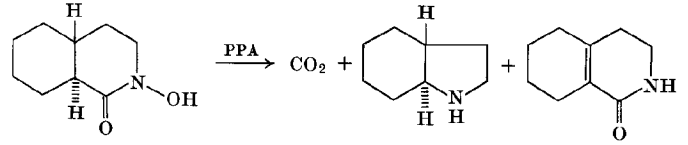
C. Reactions in Acidic and Basic Media

The hydroxamic acid function in most alicyclic and aromatic compounds is stable to hot dilute acid or alkali, and derivatives cannot undergo normal base-catalyzed Lossen rearrangement. Di Maio and Tardella,[112, 113] however, have shown that some alicyclic hydroxamic acids when treated with polyphosphoric acid (PPA) at 175°–195° undergo loss of CO, CO_2, or H_2O, in a series of reactions which must involve early fission of the N—O bond, presumably in a phosphorylated intermediate. Thus, 1-hydroxy-2- piperidone(**108**) gave carbon monoxide, 1-pyrroline (**119**), and the lactams (**120** and **121**). The saturated lactam is believed to be derived from disproportionation of the unsaturated lactam.



(**108**) (**119**) (**120**) (**121**)

The bicyclic compound (**76**) gave carbon dioxide, the saturated amine (**122**), and the unsaturated lactam (**123**).



(**76**) (**122**) (**123**)

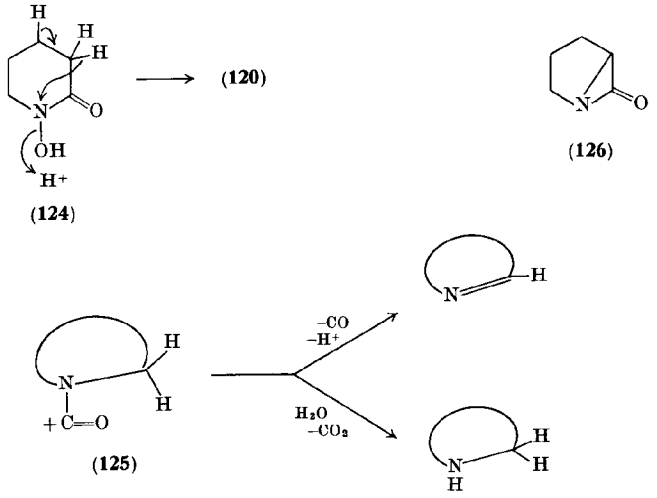
Di Maio and Tardella have proposed the process (**124** → **120**) and the ring-contracted intermediate (**125**) as being involved in these changes, but they were unable to give a detailed explanation of the

[111] H. O. House and R. W. Magin, *J. Org. Chem.* **28**, 647 (1963).

[112] G. Di Maio and P. A. Tardella, *Proc. Chem. Soc.* p. 224 (1963).

[113] G. Di Maio and P. A. Tardella, *Gazz. Chim. Ital.* **94**, 578, 584 (1964).

difference between the behavior of compounds **118** and **76**. They suggested that the formation of 1-pyrroline requires the breaking of an equatorial C-3–H bond to be concerted with the breaking of the N—O bond.

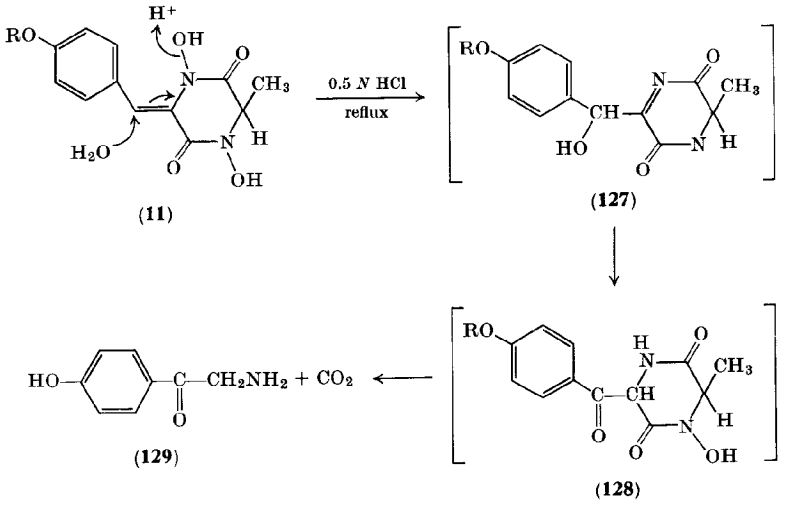


In the view of the present authors the involvement of an α-lactam intermediate[114, 115] (**126**) in a process reminiscent of the Favorskii reaction must at least be considered.

A striking case of the instability of a cyclic hydroxamic acid to both acid and base is that of the mold metabolite mycelianamide (**11**).[24, 25] Hydrolysis of mycelianamide with 0.5 *N* HCl gave the amino ketone (**129**), ammonia, carbon dioxide, and some alanine. Mild alkaline hydrolysis gave *p*-geranyloxybenzoic acid ("*p*-myceloxybenzoic acid") and treatment with ammonia gave the corresponding benzamide. Both these reactions involve an apparent rearrangement of oxygen from nitrogen to carbon, and this led to an early incorrect formulation[24] of the heterocyclic part of the molecule. The acidic hydrolysis leading to **129** is most plausibly formulated as shown below. This implies that the ammonia must be derived from

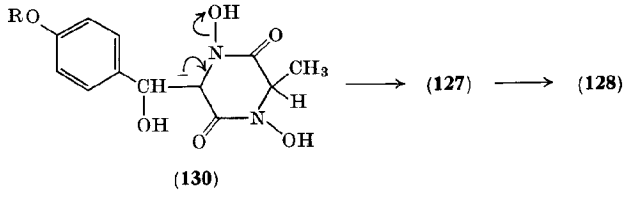
[114] J. C. Sheehan and I. Lengyel, *J. Am. Chem. Soc.* **86**, 746, 1356 (1964); *J. Org. Chem.* **31**, 4244 (1966).

[115] H. E. Baumgarten, J. F. Fuerholzer, R. D. Clark, and R. D. Thompson, *J. Am. Chem. Soc.* **85**, 3303 (1963).



the *N*-hydroxyalanine portion of the molecule; the formation of *N*-hydroxyalanine has not been reported. It is possible that breaking of the N-4—OH bond is assisted by relief of steric strain due to the *cis*-aryl-N—OH interaction in **11**.[116]

The alkaline fission may be represented similarly. β-Addition of hydroxide ion to the benzylidene double bond would lead to **130** which by a rather surprising elimination of the *N*-hydroxyl group could give the acyl dioxopiperazine (**128**). Cleavage of **128** by ammonia to give a benzamide is unexceptional. Birch *et al.*[25] noted in 1956 that no

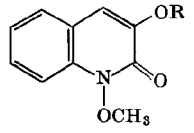


close analogies existed for these rearrangements, and this comment still appears valid.

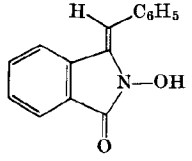
[116] R. F. C. Brown and G. V. Meehan, *Australian J. Chem.* **21**,1581 (1968).

D. Alkylation: Reactions of Alkyl and Acyl Derivatives

Cyclic hydroxamic acids and *N*-hydroxyimides are sufficiently acidic to be *O*-methylated with diazomethane, although caution is necessary because complex secondary reactions may occur. *N*-Hydroxyisatin (**105**) reacted with diazomethane in acetone to give[117] the products of ring expansion and further methylation (**131**, R = H or CH_3). The benzalphthalimidine system (**132**) could not be methylated satisfactorily with diazomethane, but the *N*-methoxy compound was readily obtained[118] by alkylation with methyl iodide and potassium carbonate in acetone. In the pyridine series, 1-benzyloxy and 1-allyloxy-2-pyridones were formed by thermal isomerization[119] of the corresponding 2-alkyloxypyridine *N*-oxides at 100°.



(131)

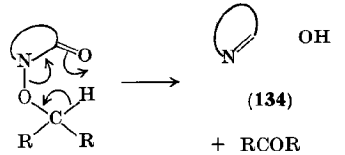


(132)

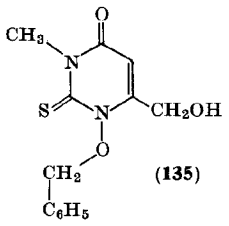
This alkyl migration is believed to proceed via ion-pair formation. These and many other simple *O*-alkylated cyclic hydroxamic acids are thermally stable[120] below 180°.

However, the *O*-alkyl derivatives are potentially unstable with respect to thermal elimination of a carbonyl compound and consequent reduction to the corresponding lactam. A combination of steric and electronic factors may permit this decomposition, i.e., **133** → **134**, to occur at quite moderate temperatures.[120] The *O*-methyl derivative of the benzalphthalimidine (**132**) undergoes slow loss of formaldehyde at 177° ($T_{1/2}$ in dimethyl sulfoxide 40 minutes), but this elimination is much faster in certain thiohydroxamic acid derivatives, e.g., **135**, which lose benzaldehyde readily at 139° in dimethyl sulfoxide ($T_{1/2}$ 6 minutes). The outstanding example of this decomposition, however,

[117] F. Arndt, J. Amende, and W. Ender, *Monatsh. Chem.* **59**, 210 (1932).
[118] R. F. C. Brown and G. V. Meehan, unpublished observations, 1967.
[119] F. J. Dinan and H. Tieckelman, *J. Org. Chem.* **29**, 1650 (1964).
[120] R. F. C. Brown, E. N. Cain, G. V. Meehan, and R. N. Warrener, *Tetrahedron Letters* p. 5249 (1967).

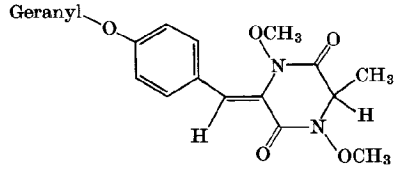


(133) (134) + RCOR



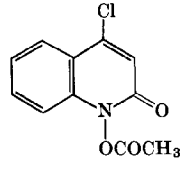
(135)

is that of the dimethyl ether (**136**) of mycelianamide, which in benzene at 65° undergoes selective loss of the N-4 methoxyl group as formaldehyde ($T_{1/2}$ 1.2 hours).[116] It is probable that steric strain due to the *cis*-aryl-*N*-methoxyl interaction is relieved in the transition state for this ready elimination.



(136)

Acyl derivatives of cyclic hydroxamic acids, like all *O*-acyl derivatives of hydroxylamine, show[121] infrared absorption because of the acyl carbonyl at characteristically high frequencies, generally near 1800 cm^{-1}.[121] The range of frequencies is similar to that found for acid chlorides, and these derivatives are also powerful acylating agents. The 1-acetoxyquinolone (**137**) is a selective reagent for the monoacetylation of *cis*-glycols; uridine is converted to 3′-*O*-acetyluridine (67%) when heated with **137** in pyridine.[122] *N*-Hydroxy-



ν_{acetyl} 1800 cm^{-1}

(137)

[121] J. P. Freeman, *J. Am. Chem. Soc.* **80**, 5954 (1958).
[122] Y. Mizumo, T. Itoh, and H. Tagawa, *Chem. Ind.* (*London*) p. 1498 (1965).

phthalimide[123] and *N*-hydroxysuccinimide[124] have been acylated with *N*-protected α-amino acids in the presence of dicyclohexylcarbodiimide to give active esters of considerable value in peptide synthesis, and similar use of active esters derived from 1-hydroxy-2-pyridone has been suggested.[125]

V. Physical Properties

A. Spectra and pK_a Values

The presence of a cyclic hydroxamic acid function in a molecule is most readily recognized by the red or violet color given with ferric chloride and by the characteristic changes in the infrared spectra of the alkyl and acyl derivatives with respect to the spectrum of the free acid. The carbonyl absorption frequencies of cyclic hydroxamic acids are generally lower than those of the corresponding lactams, and the differences are generally greater for six-membered than for five-membered systems, probably because of more effective intramolecular hydrogen bonding in the former compounds. The carbonyl absorption is shifted to higher frequencies on alkylation, and to still higher frequencies on acylation. In Table I are grouped infrared absorption maxima and some pK_a values for representative hydroxamic acids. The acidities of the alicyclic compounds appear to be similar to those of acyclic hydroxamic acids[126] (cf. acethydroxamic acid, pK_a 9.40, and benzohydroxamic acid, pK_a 8.75), but the *N*-hydroxyimides and the aromatic compounds are considerably more acidic. Ultraviolet spectra are not surveyed because the hydroxamic acid group itself has no useful characteristic absorption in most systems. Ultraviolet spectra of the acids and alkyl derivatives have been widely used in the aromatic series to show that compounds such as **3** exist mainly in the 1-hydroxy-2-pyridone form rather than as the tautomer, 2-hydroxypyridine 1-oxide. The C-8 protons in the NMR spectra of a series of *N*-hydroxyisocarbostyrils (**95**) are strongly deshielded with respect to the C-5, C-6, and C-7 protons because of the magnetic anistropy of the *peri*-carbonyl group. Moriconi and Creegan[94] compared the NMR and

[123] G. H. L. Nefkens, G. I. Tesser, and R. J. F. Nivard, *Rec. Trav. Chim.* **81**, 683 (1962).
[124] G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Am. Chem. Soc.* **86**, 1839 (1964).
[125] L. A. Paquette, *J. Am. Chem. Soc.* **87**, 5186 (1965).
[126] W. Cohen and B. F. Erlanger, *J. Am. Chem. Soc.* **82**, 3928 (1960).

TABLE I
Infrared and pK_a Data

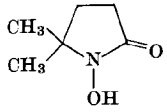
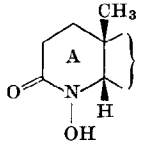
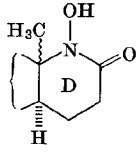
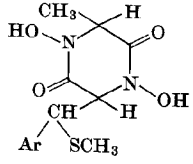
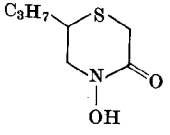
Structure	ν OH	ν Ring C=O	ν Ester C=O	State	pK_a	Ref.
	3320, 3090	1678	—	Mull	8.7	74
	3240	1623	—	CCl_4	—	53
Methyl ether	—	1658	—	CCl_4	—	53
Benzoate	—	1677	1720[a]	CCl_4	—	53
 (8 examples)	3280–3050	1661–1634	—	Mull	—	99
Acetates	—	1695–1678	1799–1786	Mull	—	99
	3175	1665	—	Mull	—	116
Dimethyl ether	—	1685	—	Mull	—	116
Diacetate	—	1700	1800	Mull	—	116
	—	1580[a]	—	—	—	48

TABLE I—*continued*

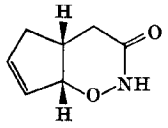
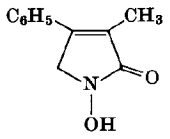
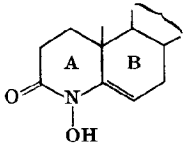
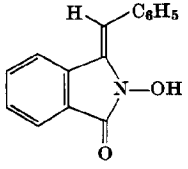
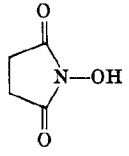
Structure	ν OH	ν Ring C=O	ν Ester C=O	State	pK$_a$	Ref.
	—	1670	—	Mull	—	97
	—	1667	—	KBr	—	127
Acetate	—	1695	1792	KBr	—	127
 λ_{max} 238 mμ, Log ϵ 4.17	3390, 3310	1630	—	KBr	—	54
Benzyl ether	—	1667	—	KBr	—	54
	—	1685	—	Mull	—	120
Methyl ether	—	1710	—	Mull	—	120
	—	1789, 1709	—	Mull	6.0	43

TABLE I—*continued*

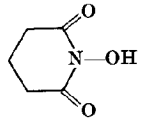
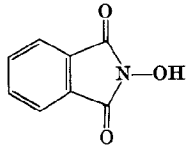
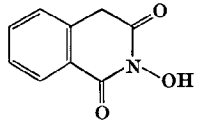
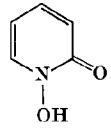
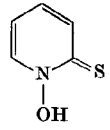
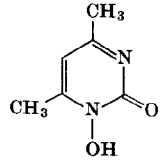
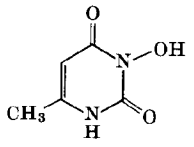
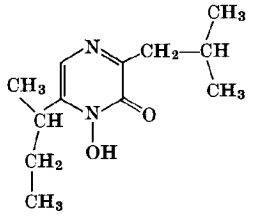
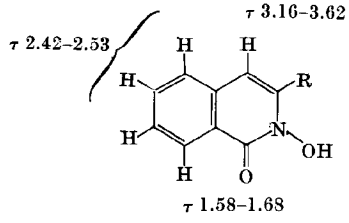
Structure	ν OH	ν Ring C=O	ν Ester C=O	State	pK$_a$	Ref.
	—	1742, 1672	—	Mull	7.6	43
	—	1795, 1745	—	Mull	—	44
Acetate	—	1792, 1751	1821	Mull	7.0[b]	44
	—	1727, 1667	—	Mull	8.0[c]	44
	2400	1655	—	$CHCl_3$	—	128
	—	—	—	—	5.9	64
Methyl ether	—	1664	—	—	—	128
Acetate	—	1665	1800	—	—	125
Benzoate	—	1670	1780	—	—	125
	2600	—	—	$CHCl_3$	4.67	128
	—	1750(w), 1700	—	Mull	6.1	129

TABLE I—*continued*

Structure	ν OH	ν Ring C=O	ν Ester C=O	State	pK_a	Ref.
	—	—	—	—	7.11	130
	—	1640	—	KBr	—	18
	—	—	—	—	5.5	131

[a] This carbonyl frequency is, in the opinion of the present authors, unexpectedly low.
[b] Measured in 50% methanol.
[c] Measured in 50% dimethylacetamide.

ultraviolet spectra of the *N*-hydroxy compounds with those of 2,3-dimethylisocarbostyril and concluded that compounds (**95**) exist predominantly in the *N*-hydroxylactam form.



(**95**)

[127] J. A. Moore and J. Binkert, *J. Am. Chem. Soc.* **81**, 6031 (1959).
[128] R. A. Jones and A. R. Katritzky, *J. Chem. Soc.* p. 2937, 2947 (1960).
[129] G. Zvilichovsky, *Tetrahedron* **23**, 353 (1967).
[130] A. Cossey, J. N. Phillips, and J. S. Shannon, unpublished observations, 1967.
[131] J. D. Dutcher, *J. Biol. Chem.* **232**, 785 (1958).

B. Mass Spectra

There has as yet been no systematic work on the mass spectra of cyclic hydroxamic acids, but from the limited information available the direct loss of O or OH from the molecular ion is to be expected. The fragmentation behavior of the *O*-alkyl derivatives is rather unpredictable, although again processes involving fission of the N—O bond are generally important. Table II shows the prominent first-generation fragment ions from a few hydroxamic acids and their ethers.

TABLE II
Mass Spectra

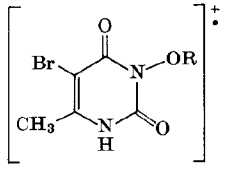
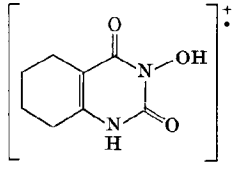
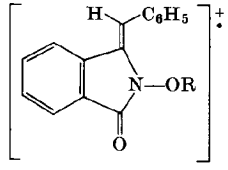
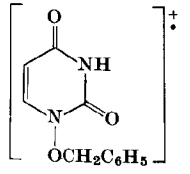
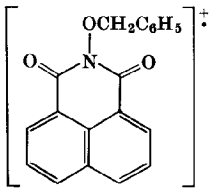
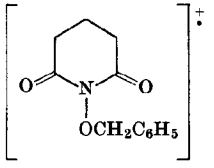
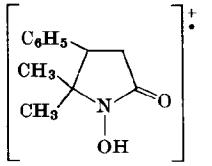
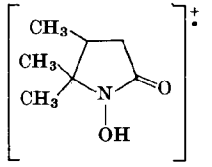
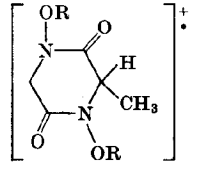
Structure		Ref.
	R = H → $[M - O]^{+\cdot}$ R = CH_3 → $[M - CH_2O]^{+\cdot}$ R = C_2H_5 → $[M - C_2H_4]^{+\cdot}$ and $[M - CH_3CHO]^{+\cdot}$	130
	→ $[M - OH]^{+}$	130
	R = H → $[M - O]^{+\cdot}$ and $[M - OH]^{+}$ R = CH_3 → $[M - CH_3]^{+}$ and $[M - OCH_3]^{+}$	132
	→ $C_7H_7^{+}$; $[M - C_6H_5CHO]^{+\cdot}$ very weak	132

TABLE II—*continued*

Structure		Ref.
	→ $[M - C_6H_5CHO]^{+\cdot}$ and $C_7H_7^+$	132
	→ $C_6H_5CH{=}\overset{+}{O}H$ and $[M - C_6H_5CO]^+$	132
	→ $[M - CH_3]^+$, $[M - O]^{+\cdot}$, and $[M - CH_3, O]^+$	132
	→ $[M - CH_3]^+$ and $[M - CH_3, O]^+$	132
	R = H → $[M - O]^{+\cdot}$, $[M - OH]^+$, and $[M - CO]^{+\cdot}$ R = CH_3 → $[M - CO]^{+\cdot}$ and $[M - OCH_3]^+$	132

[132] D. St. C. Black, R. F. C. Brown, E. N. Cain, G. V. Meehan, and R. N. Warrener, unpublished observations, 1967.

Pyrylium Salts

Part I. Syntheses

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I. Introduction

A. Scope of the Review

As yet no extensive review on monocyclic pyrylium salts has been published, although these salts represent one of the fundamental heterocyclic systems and are the basis of important natural products

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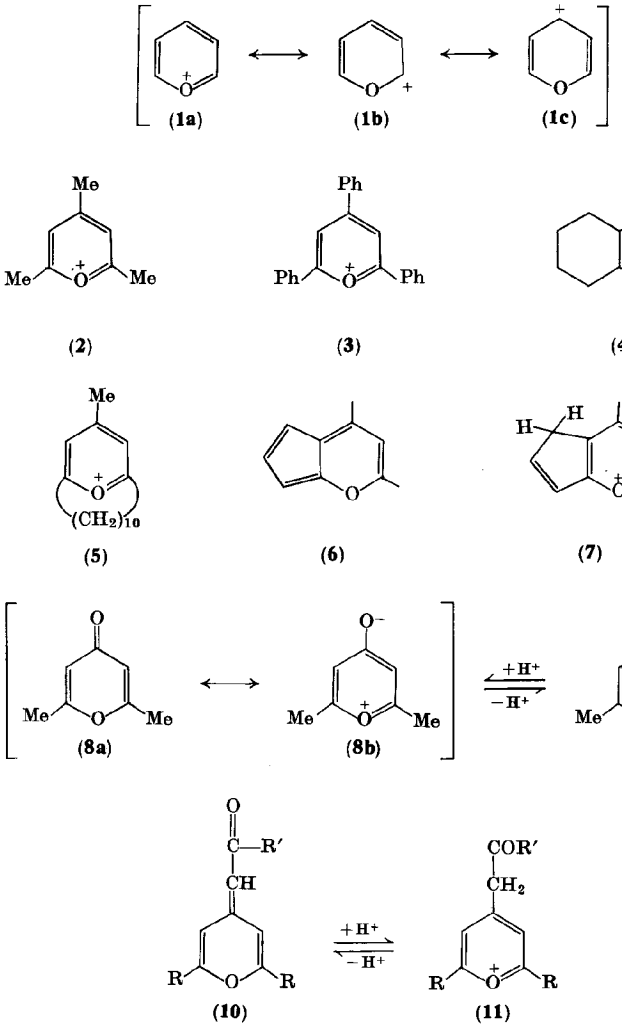
such as the anthocyanins.[1] Texts published in treatises or monographs on organic chemistry[2] or heterocyclic chemistry[3–8] are very restricted. Reviews on pyrones,[9,10] oxygen heterocycles,[11,12] or aliphatic acylations,[13,14] or reactions catalyzed by perchloric acid[15,16] cover marginal topics. There are only two recent reviews pertinent to this field, namely the excellent review by Dimroth[17] which is concerned only with the conversion of pyrylium salts into aromatic

[1] F. M. Dean, "Naturally Occuring Oxygen Ring Compounds" Butterworth, London and Washington, D.C., 1963.
[2] N. Campbell, *in* "Chemistry of Carbon Compounds" (E. H. Rodd, ed.), Vol. IVB, p. 809. Elsevier, Amsterdam, 1959.
[3] J. Fried, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. I, p. 343. Wiley, New York, 1950.
[4] A. A. Morton, "The Chemistry of Heterocyclic Compounds." McGraw-Hill, New York, 1946.
[5] A. Albert, "Heterocyclic Chemistry," Oxford Univ. Press (Athlone), London and New York, 1959; 2nd Ed., 1968.
[6] A. R. Katritzky and J. M. Lagowski, "Heterocyclic Chemistry." Methuen, London and Wiley, New York, 1960.
[7] G. M. Badger, "The Chemistry of Heterocyclic Compounds." Academic Press, New York, 1961.
[8] R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds." Wiley (Interscience), New York, 1960.
[9] L. A. Cavalieri, *Chem. Rev.* **41**, 525 (1947).
[10] N. P. Shusherina, N. D. Dmitrieva, E. A. Lukyanets, and R. Y. Levina, *Usp. Khim.* **36**, 437 (1967).
[11] R. D. Topsom, *Rev. Pure Appl. Chem.* **14**, 127 (1964).
[12] H. Meerwein, *in* "Houben-Weyl's Methoden der Organischen Chemie" (E. Müller, ed.), Vol. VI/3, pp. 352–365. Thieme, Stuttgart, 1965; W. Lürken and E. Müller, *in* "Houben-Weyl's Methoden der Organischen Chemie" (E. Müller, ed.), Vol. VI/4, p. 100. Thieme, Stuttgart, 1966.
[13] C. D. Nenitzescu and A. T. Balaban, *in* "Friedel-Crafts and Related Reactions" (G. A. Olah, ed.), Vol. III, Chap. 37. Wiley (Interscience), New York, 1964.
[14] P. F. G. Praill, "Acylation Reactions," Chapt. 5, p. 73. Macmillan (Pergamon), New York, 1963.
[15] G. N. Dorofeenko, S. V. Krivun, V. I. Dulenko, and Y. A. Zhdanov, *Usp. Khim.* **34**, 219 (1965).
[16] G. N. Dorofeenko, Y. A. Zhdanov, V. I. Dulenko, and S. V. Krivun, "Khlornaya kislota i ee soedineniya v organicheskom sinteze," Izd. Rostovsk. Univ., Rostov/Don, 1965.
[17] K. Dimroth, *Angew. Chem.* **72**, 331 (1960); K. Dimroth and K. H. Wolf, "Newer Methods of Preparative Organic Chemistry," Vol. 3, p. 357. Academic Press, New York, 1964; "Neuere Methoden der präparativen organischen Chemie," Vol. 3, p. 261. Verlag Chemie, Weinheim, 1960.



compounds, and the review by Balaban and Nenitzescu[18] on investigations in the class of pyrylium salts, which is not widely accessible.

The present review, which extends and brings up to date a previous one,[19] covers only monocyclic pyrylium salts, e.g., **1a**, **b**, **c** and **2**. The term "monocyclic" is here meant to imply that there are no fused six-membered aromatic rings on the pyrylium cation which could allow an extended conjugation. Therefore, benzo derivatives such as benzopyrylium (chromylium, flavylium, etc.), isobenzopyrylium, dibenzopyrylium salts (xanthylium, naphthopyrylium, etc.) are not discussed here. However, pyrylium salts bearing aromatic or heterocyclic substituents, e.g. **3**, or possessing fused saturated rings, e.g., **4** and **5**, are also reasonably considered as monocyclic pyrylium salts and are included in the present review. Pseudo azulenes such as **6** are also discussed here insofar as they are anhydro bases of the corresponding monocyclic pyrylium salts (**7**), in which there is no continuous conjugation in the fused five-membered ring.

From the same point of view, 4-pyrones (**8a**) or 2-pyrones are anhydro bases of 4-hydroxypyrylium (**9**) or 2-hydroxypyrylium salts. Vinylogs (**10**) and phenylogs (**12**) (violones, after Dilthey and Burger[20]) of these systems are known, whose conjugate acids are monocyclic pyrylium salts (**11** and **13**).

The literature search is complete through 1968, and some 1969 references have also been included.

(12) (13)

B. Nomenclature and Formulation

The name pyrylium has been singularly contested by those who first studied it in the past. This name, pyrylium (which has been written pyrilium of pyryllium), was proposed by Decker and von Fellenberg[21]

[18] A. T. Balaban and C. D. Nenitzescu, *Rev. Chim. Acad. Rep. Populaire Roumaine* **6**, 269 (1961); *Studii Cercetari Chim., Acad. Rep. Populaire Romania* **9**, 251 (1961).

[19] W. Schroth and G. Fischer, *Z. Chem.* **4**, 281 (1964).

[20] W. Dilthey and B. Burger, *Ber. Deut. Chem. Ges.* **54**, 825 (1921).

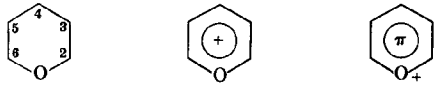
[21] H. Decker and T. von Fellenberg, *Ann. Chem.* **356**, 281 (1907); **364**, 1 (see p. 37) (1908).

(they actually proposed phenopyrylium, for what we now call benzopyrylium) in 1907–1908. Two years later, Baeyer tried to replace this name by pyroxonium because "pyrylium offers no fulcrum to the memory."[22] Later, Dilthey proposed several other names: pyrylenium, pyronium, and pyrenium. He argued[23] the pyrenium is the best name because pyronium or pyroxonium suggest pyrone salts, while pyrylium or pyrylenium suggest similarity with the pyrryl (pyrrole) radical. However, the name pyrylium had already gained general acceptance.

The *Chemical Abstracts* nomenclature will be adopted, but when common trivial names are available, these will also be employed, e.g., 4-pyrone along with 4*H*-pyran-4-one. Unlike *Chemical Abstracts*, thio will be used to designate a thione and thia will imply a sulfur heteroatom.

According to *Chemical Abstracts*, the pyrylium ring is numbered as shown in formula **14**. Positions 2 and 6 may also be denoted by α, positions 3 and 5 by β, and position 4 by γ, as in pyridine.

The commonly employed benzenelike oxonium formula (**1a**) will be used in preference to other proposed formulations (**15** or **16**), although all reactions of pyrylium salts involve carbonium structures (**1b** or **1c**).



(14) (15) (16)

The pyrylium cation possesses, according to the substituents in positions 2, 4, and 6, a more or less pronounced electrophilic reactivity which enables it to add nucleophiles in these positions. According to the nucleophilic reactivity[24,25] and the carbon basicity[25–27] of the anions, an ion pair (a substituted pyrylium cation and an anion: halide, perchlorate, sulfate, fluoroborate, chloroferrate, etc.), or a covalently bonded 2*H*- or 4*H*-pyran may be formed. With the more basic anions

[22] A. Baeyer, *Ber. Deut. Chem. Ges.* **43**, 2337 (1910).

[23] F. Quint and W. Dilthey, *Ber. Deut. Chem. Ges.* **64**, 2082 (1931).

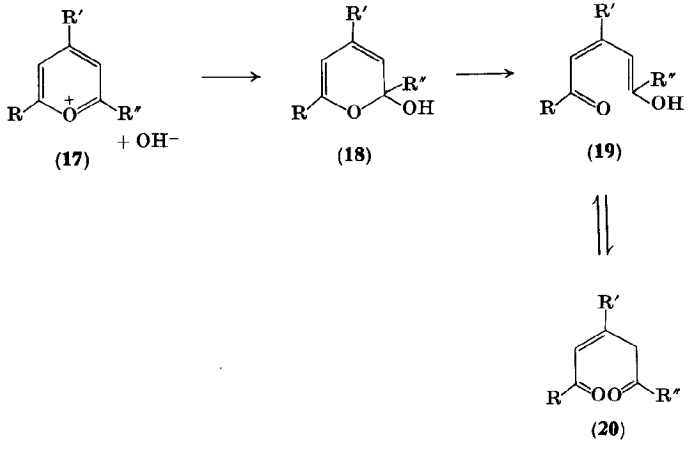
[24] J. O. Edwards and R. G. Pearson, *J. Am. Chem. Soc.* **84**, 16 (1962).

[25] J. F. Bunnett, *Ann. Rev. Phys. Chem.* **14**, 271 (1963).

[26] A. J. Parker, *Proc. Chem. Soc.* p. 371 (1961).

[27] R. Gompper, *Angew. Chem.* **76**, 412 (1964).

(softer bases[28–30]) such as hydroxyl, cyanide, carbonate, or acetate, the pyrylium salts react rapidly in two ways. If the cations possess an acid proton in a benzylic position, this is split off yielding an *anhydro base* (pyrones, pyronimines, methylenepyrans). Otherwise, addition occurs at α- or γ-positions, and a pyran is formed. In the particular case of the hydroxyl anion (**17**), the *pseudo base* thus formed may be a 4- or a 2-pyranol (nomenclature after Bülow and Wagner,[31] and Baeyer and Piccard[32]) or a ring-opened product. The



nucleophilic reactivity of the 2-position usually exceeds that of the 4-position, but the 2-pyranol (**18**) is unstable because in these unsaturated hemiketals the equilibrium is displaced toward the open-chain diketone (**19** ⇌ **20**).

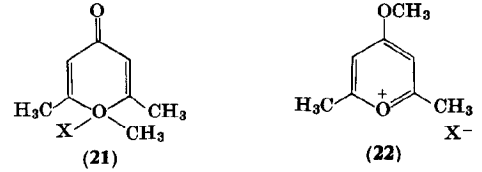
Under the influence of acids, *cis*-2-ene-1,5-diones (**20**) or their enol forms (**19**) are converted by dehydration back into pyrylium salts. Accordingly, any synthetic method resulting in 1,5-enediones is, in fact, a method for the synthesis of pyrylium salts.

[28] R. G. Pearson, *J. Am. Chem. Soc.* **85**, 3533 (1963); *Science* **151**, 172 (1966); *Chem. Brit.* **3**, 103 (1967).
[29] R. G. Pearson and J. Songstad, *J. Am. Chem. Soc.* **89**, 1827 (1967).
[30] B. Saville, *Angew. Chem.* **79**, 966 (1967).
[31] C. Bülow and H. Wagner, *Ber. Deut. Chem. Ges.* **34**, 1189 (1901).
[32] A. Baeyer and J. Piccard, *Ann. Chem.* **384**, 208 (1911).

C. Historical

The first chemists to prepare a monocyclic pyrylium salt were von Kostanecki and Rossbach[33] who in 1896 described the fluorescence in dilute aqueous solution of the reaction product obtained from 1,3,5-triphenylpentane-1,5-dione (benzylidene-diacetophenone) and sulfuric acid. However, they failed to isolate the compound which caused the fluorescence and did not suspect that it was a pyrylium salt. It was only in 1916–1917 that Dilthey[34] recognized that this fluorescence resulted from 2,4,6-triphenylpyrylium (**3**).

The puzzling discovery of Collie and Tickle[35] in 1899 that 2,6-dimethyl-4-pyrone (**8**) affords crystalline salts (**9**) with acids, which were the first monocyclic pyrylium salts to be isolated, was interpreted by a formula (**21**) with tetracovalent oxygen.[35,36] An active period of research followed. The methosulfate[37] or methiodide[38] of 2,6-dimethylpyrone was converted by ammonia into 4-methoxy-2,6-lutidine,[22] therefore, the exocyclic oxygen of the pyrone must be involved in the salt formation. Thus, formula **21** was disproved and formula **22** was demonstrated for these salts.



Baeyer and Piccard[32,39] were the first to prepare crystalline monocyclic pyrylium salts without hydroxy or alkoxy substituents, from γ-pyrones and Grignard reagents in 1911. They ascribed a correct structure to these salts, although the bonds in the ring and the valency of the oxygen heteroatom remained contested topics for the next 20 years. The discussions around the formula of pyrylium

[33] S. von Kostanecki and G. Rossbach, *Ber. Deut. Chem. Ges.* **29**, 1488 (see p. 1493) (1896).
[34] W. Dilthey, *J. Prakt. Chem.* **95**, 107 (1917).
[35] J. N. Collie and T. Tickle, *J. Chem. Soc.* **75**, 710 (1899).
[36] A. Werner, *Ber. Deut. Chem. Ges.* **34**, 3300 (1901).
[37] A. Baeyer and V. Villiger, *Ber. Deut. Chem. Ges.* **34**, 2679 (1901).
[38] F. Kehrmann and A. Duttenhöfer, *Ber. Deut. Chem. Ges.* **39**, 1299 (1906).
[39] A. Baeyer and J. Piccard, *Ann. Chem.* **107**, 332 (1915).

salts and pyrones,[2] which grouped the names of Collie,[35] Baeyer,[37,39] Werner,[36] Dilthey,[40] Kehrmann,[41] Hantzsch,[42] Arndt,[43] Eistert,[44] Robinson,[45] etc., lead eventually to the theory of mesomerism and resonance and thus were an important step in the development of theoretical chemistry.

For the preparation of larger amounts of pyrylium salts the method of Baeyer and Villiger[37] was unsuitable. Therefore, the discovery by Dilthey[46] of new convenient methods for preparing aryl-substituted pyrylium salts in 1916 was an important event. By the studies of Dilthey, and a little later, of Schneider, many reactions of aryl-substituted pyrylium salts were discovered.

It must be taken into account that in all papers published between 1916 and 1922 the structure of methyldiarylpyrylium salts is erroneously indicated as a symmetrical 2,6-diaryl-4-methylpyrylium structure. The unsymmetrical structure (2,4-diaryl-6-methyl) was recognized by Gastaldi,[47,48] then by Schneider and Ross,[49] and finally by Dilthey and Fischer.[50]

Recent important developments consist in the synthesis of the unsubstituted pyrylium cation by Klages and Träger, the preparation of pyrylocyanines by Wizinger, the development of simple syntheses for alkyl-substituted pyrylium salts by Balaban and Nenitzescu, Praill, Schroth and Fischer, Schmidt, and Dorofeenko, the discovery of a variety of reactions by Dimroth and Hafner, and the study of physical properties by Balaban.

The statistics of the number of publications devoted to pyrylium salts, and of new pyrylium salts reported, show that after the rapid development of the field in 1917–1924, there was a lack of interest

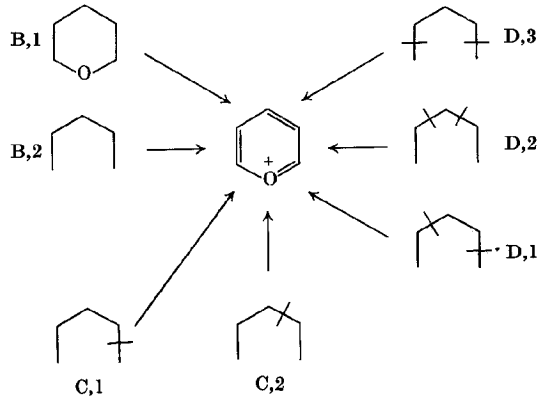
[40] W. Dilthey, *Ber. Deut. Chem. Ges.* **53**, 261 (1920).
[41] F. Kehrmann, *Ber. Deut. Chem. Ges.* **54**, 657 (1921).
[42] A. Hantzsch, *Ber. Deut. Chem. Ges.* **49**, 54 (1916).
[43] F. Arndt, E. Scholz, and P. Nachtwey, *Ber. Deut. Chem. Ges.* **57**, 1903 (1924); F. Arndt and L. Lorenz, *Ber. Deut. Chem. Ges.* **63**, 3121 (1930).
[44] B. Eistert, "Tautomerie und Mesomerie, Gleichgewicht und Resonanz," p. 64. Enke, Stuttgart, 1938.
[45] J. W. Armit and R. Robinson, *J. Chem. Soc.* **127**, 1604 (1925).
[46] W. Dilthey, *J. Prakt. Chem.* **94**, 53 (1916).
[47] C. Gastaldi, *Atti Accad. Nazl. Lincei, Rend. Classe Sci. Fis. Mat. Nat.* **31**, 257 (1922); *Gazz. Chim. Ital.* **52**, I, 169 (1922); *Chem. Abstr.* **16**, 2515 (1922).
[48] C. Gastaldi, *Gazz. Chim. Ital.* **64**, 234 (1934); *Chem. Abstr.* **28**, 5069 (1934).
[49] W. Schneider and A. Ross, *Ges. Deut. Chem. Ges.* **55**, 2775 (1922).
[50] W. Dilthey and J. Fischer, *Ber. Deut. Chem. Ges.* **56**, 1012 (1923).

toward these compounds until 1959 when a very marked new increase can be observed. Therefore, a review that would sum up the wide amount of new data obtained in the last 9 years is timely.

II. Syntheses

A. Classification

As mentioned previously, pyrylium salts are dehydration products of the conjugate acids of *cis*-2-ene-1,5-diones, and therefore, most syntheses of pyrylium salts are, in fact, syntheses of 1,5-enediones. Dilthey[46] has devised his new pathways to pyrylium salts by analogy



Scheme 1. Classification of syntheses.

with pyridine syntheses, and he expressed the view that the syntheses of pyridine which are carried out in the presence of ammonia proceed through the intermediacy of pyrylium salts or 1,5-enediones.

The syntheses of pyrylium salts will be classified into three groups, according to the number of building blocks required to form the ring in a one-step process (see Scheme 1).

One-component syntheses, in which a pyran ring (type B,1) or a 1,5-dione structure (type B,2) is already present.

Two-component syntheses, in which the five-membered carbon chain can be formed in two ways: 1+4 (type C,1) or 2+3 (type C,2).

Three-component systems, in which the five-membered carbon chain can be formed 1+2+2 (types D,1 and D,2) or 1+1+3 (type D,3).

In the three-component syntheses, only those cases are of practical importance in which the two two-carbon fragments in types D,1 and D,2 or the two one-carbon fragments in type D,3, are identical; in these cases there are thus only two, not three, reagents. Actually all known syntheses pertaining to group D satisfy this condition. This requirement also explains why no example for a fourth imaginable[51] type D,4, for the two imaginable four-component syntheses E,1 and E,2 or for the five-component synthesis F,1 is known and is unlikely to be found; in these cases at least three reagents are necessary, therefore complex mixtures are expected to result and the procedure is unpractical.

It will be observed that most syntheses yield pyrylium salts in which positions 2,4, and 6 are substituted. Since according to formulas **1b–1c** these positions have a partial positive charge, it can readily be understood why electron-donating substituents (hydroxy, alkoxy, alkyl, or aryl) in these positions stabilize the pyrylium salts. Only three pyrylium salts which do not have substituents in either α-position have been reported and few unsubstituted in γ or in one α-position; they are less stable toward hydrolysis, and in the case of perchlorates they explode more easily, than 2,4,6-trisubstituted compounds. In fact, the former are secondary, the latter tertiary carbonium ions. This fact also explains why the parent compound (**1**) was prepared only in 1953.

B. One-Component Syntheses

1. *From Compounds with Preformed Pyran Ring*

a. *From a Different Pyrylium Salt.* To this section pertain all reactions which convert one pyrylium salt into another. This does not include, however, 2- or 4-pyrones which behave according to formula

[51] The potential of the positive integer 5, i.e., the seven different ways it can be obtained as sum of positive integers, is represented by: 5 (type B syntheses); 4+1, 3+2 (type C); 2+2+1, 3+1+1 (type D); 2+1+1+1 (type E); and 1+1+1+1+1 (type F). (G. H. Hardy and E. M. Wright, "An Introduction to the Theory of Numbers," Chapt. 19, 3rd Ed. Oxford Univ. Press, London and New York, 1954.)

8b as pyrylium oxides, just like the phenolate anion which is a benzene oxide, or like tropone which is a tropylium oxide.

First, mention should be made of the metathetical reaction, *replacing an anion of a pyrylium salt by another*; when the solubility of the latter salt is lower than that of the former, the conversion is easy. In the opposite case, one has to find a solvent in which the solubilities are reversed (perchlorates are less soluble in water than chloroferrates or iodides, but in concentrated hydrochloric or hydroidic acids, respectively, the situation is reversed[52, 53]). For preparing chlorides which are usually readily soluble salts, one can treat the less soluble chloroferrates with hydrogen sulfide[53] or hydroxylamine.[54] Another method is to obtain the pseudo base in an organic solvent and to treat it with an anhydrous acid.[53]

Most reactions are carried out with perchlorates or fluoroborates; methylene dichloride is a convenient aprotic solvent for salts with the former anion. Among the various anions, the strongest nucleophile yet reported to give ionized salts (in the case of an isobenzopyrylium salt) is the formate anion[55] (cf. also Section II, B, 2, c).

Second, there exists a number of reactions starting from pyrylium salts and involving substitution at the pyrylium ring, or modification of existing substituents. These reactions will be described here briefly; they will be discussed in more detail in the forthcoming second part of this review.

Only one *electrophilic substitution*[56] *at the pyrylium ring* has been described, namely the β-deuteration of 2,4,6-trimethylpyrylium[57] or 2,4,6-triphenylpyrylium perchlorates[58] on prolonged reflux in CH_3COOD; possibly, however, this reaction proceeds via the pseudo base. The nitration of 2,4,6-triphenylpyrylium does not affect the pyrylium ring, but attacks the 2- and 6-phenyl groups in the *meta*-, and the 4-phenyl group in the *para*-position, as was proved by

[52] A. T. Balaban and C. D. Nenitzescu, *J. Chem. Soc.* p. 3553 (1961).
[53] A. T. Balaban, *Compt. Rend.* **256**, 4041 (1963).
[54] N. V. Khromov-Borisov and L. A. Gavrilova, *Zh. Obshch. Khim.* **31**, 2192 (1961).
[55] M. Lempert-Sreter, *Acta Chim. Acad. Sci. Hung.* **50**, 379 (1966).
[56] A. R. Katritzky and C. D. Johnson, *Angew. Chem.* **79**, 629 (1967).
[57] E. Gârd, A. Vasilescu, G. D. Mateescu, and A. T. Balaban, *J. Labelled Comds*, **3**, 196 (1967).
[58] E. Gârd, I. I. Stănoiu, F. Chiraleu, and A. T. Balaban, *Rev. Roumaine Chim.* **14**, 247 (1969).

Le Fèvre, both by degradation and by synthesis.[59–61] The course of the substitutions described above was accounted for by molecular orbital calculations.[62, 63]

Less reactive electrophilic reagents like those involved in acylation or alkylation apparently do not react with phenyl-substituted pyrylium salts; the *p*-acylation of a phenyl group in position 3 of the pyrylium salt obtained on diacylation of allylbenzene (Section II,D,3,a), and the *p*-*t*-butylation of phenyl groups in γ-positions of pyrylium salts prepared by dehydrogenation of 1,5-diones by means of *t*-butyl cations (Section II,B,2,f) probably occur in stages preceding the pyrylium ring closure.

Nucleophilic displacements at alkoxypyrylium salts will be described in Section II,B,1,c.

As *modification of substituents*, the simplest is the deuteration of alkyl groups bonded to positions 2, 4, and 6 of the pyrylium nucleus on recrystallization from deuterium oxide or from CH_3COOD. Since only benzylic hydrogens are exchanged, the intermediates[63a] are probably methylenepyrans (anhydro bases). A study by means of NMR spectroscopy showed that the 4-methyl group reacts 10 times faster than the 2- and 6-methyl groups in 2,4,6-trimethylpyrylium, allowing selective deuteration and/or dedeuteration,[57, 58] and that diphenylmethylpyrylium salts are deuterated even faster.[64] Molecular orbital calculations substantiate these findings.[62, 63] The deuterated or partly deuterated 2,4,6-trimethylpyrylium salts are useful starting materials for the preparation of aromatic or heterocyclic compounds with deuterated side-chains difficultly obtainable by direct exchange.[65, 66] The easy formation of the anhydro bases from 2- and

[59] R. J. W. Le Fèvre and J. Pearson, *J. Chem. Soc.* p. 1197 (1933).
[60] H. E. Johnston and R. J. W. Le Fèvre, *J. Chem. Soc.* p. 2900 (1932).
[61] C. G. Le Fèvre and R. J. W. Le Fèvre, *J. Chem. Soc.* p. 2894 (1932).
[62] C. C. Renția, A. T. Balaban, and Z. Simon, *Rev. Roumaine Chim.* **11**, 1193 (1966).
[63] G. V. Boyd, *Rev. Roumaine Chim.* **12**, 1133 (1967).
[63a] D. Fărcasiu and E. Gârd, *Tetrahedron*, **24**, 4741 (1968).
[64] E. Gârd, I. Bally, A. Vasilescu, A. Arsene, and A. T. Balaban, *J. Labelled Comds.* **1**, 182 (1965).
[65] A. T. Balaban, E. Gârd, A. Vasilescu, and A. Barabas, *J. Labelled Comds.* **1**, 266 (1965).
[66] A. Barabas, E. Gârd, A. Vasilescu, and A. T. Balaban, *J. Labelled Comds.* **2**, 359 (1966).

4-alkylpyrylium salts with benzylic hydrogenas also explains the reactivity of these salts in condensations with carbonyl or nitroso groups.

The first mention that α- or γ-methyl groups of pyrylium salts can be condensed with aromatic aldehydes was made almost simultaneously by Buck and Heilbron,[67] Schneider,[68] and Dilthey and Fischer.[69] Subsequent work[54, 70–73] evidenced the generality of the reaction with variously substituted pyrylium salts and benzaldehydes; the resulting styrylpyrylium salts can be converted into styrylpyridines.[74] Wizinger also obtained distyrylpyrylium salts from 2,6-dimethyl-4-phenylpyrylium and 2 moles of benzaldehyde,[75] whereas Kelemen and Wizinger[76–78] condensed alkylpyrylium salts with pyrones obtaining pyrylocyanines[79] (cf. also Section II,B,1,d). Styrylpyrylium salts obtained from aldehydes[80–83] or dialdehydes[83] can also be converted into stilbene derivatives.[84, 85] The "active" methyl groups of

[67] J. S. Buck and I. M. Heilbron, *J. Chem. Soc.* **123**, 2521 (1923).
[68] W. Schneider, *Ann. Chem.* **432**, 297 (1923).
[69] W. Dilthey and J. Fischer, *Ber. Deut. Chem. Ges.* **57**, 1653 (1924).
[70] F. M. Hamer, I. M. Heilbron, J. H. Reade, and H. N. Wells, *J. Chem. Soc.* p. 251 (1932).
[71] T. R. Thompson, U.S. Patent No. 2,461,484 (Feb. 8, 1949); *Chem. Abstr.* **43**, 6100 (1949).
[72] H. Brockmann, *Ber. Deut. Chem. Ges.* **77**, 347, 529 (1944).
[73] A. I. Tolmachev and V. P. Sribnaya, *Zh. Obshch. Khim.* **35**, 316 (1965); A. I. Tolmachev, *Zh. Obshch. Khim.* **33**, 1864 (1963).
[74] J. L. R. Williams, R. E. Adel, J. M. Carlson, G. A. Reynolds, D. G. Borden, and J. A. Ford, *J. Org. Chem.* **28**, 387 (1963).
[75] R. Wizinger and K. Wagner, *Helv. Chim. Acta* **34**, 2290 (1951).
[76] J. Kelemen and R. Wizinger, *Helv. Chim. Acta* **45**, 1908 (1962).
[77] J. Kelemen, Ph.D. Thesis, University of Basel, 1961.
[78] J. Kelemen and R. Wizinger, *Helv. Chim. Acta* **45**, 1918 (1962).
[79] O. Riester, Ph.D. Thesis, Univ. of Bonn, 1937.
[80] G. N. Dorofeenko, O. E. Shelepin, Z. N. Nazarova, V. P. Novikov, and G. P. Tikhonova, *Zh. Obshch. Khim.* **35**, 570 (1965).
[81] G. N. Dorofeenko, Y. A. Zhadnov, V. A. Palchkov, and S. V. Krivun, *Zh. Obshch. Khim.* **36**, 1728 (1966).
[82] G. N. Dorofeenko, Y. A. Zhadnov, A. D. Semenov, V. A. Palchkov, and E. P. Olekhnovich, *Zh. Organ. Khim.* **2**, 1864 (1966).
[83] S. V. Krivun, and G. N. Dorofeenko, *Khim. Geterotsikl. Soed.* p. 656 (1966).
[84] G. N. Dorofeenko, V. V. Mezheritski, and V. I. Ardashev. *Zh. Organ. Khim.* **3**, 1853 (1967).
[85] G. N. Dorofeenko, Y. A. Zhdanov, and V. A. Palchkov, *Zh. Vses. Khim. Obshchestva im. D. I. Mendeleeva* **11**, 598 (1966).

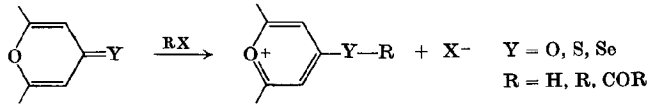
pyrylium salts can also be condensed with aryldiazonium salts,[86, 87] nitroso derivatives,[87] orthoformic esters[88, 88a] (cf. Section II,B,2,a), or methylolamines (Mannich reaction)[89] affording the corresponding modified pyrylium salts.

b. *Electrophilic Protonation, Alkylation, or Acylation of (Thio)pyrones.* 4-Pyrones and 2-pyrones have been the first starting materials for the synthesis of pyrylium salts. The preparation of 2,6-dimethyl-4*H*-pyran-4-one (**8**) from dehydroacetic acid[90] and boiling hydrochloric acid has been extensively investigated.[9, 10, 91–94] Other available 4-pyrones are 2,6-diphenyl-4-pyrone,[95, 96] 3,5-dibenzyl-4-pyrone,[97] unsubstituted 4-pyrone,[98–101] and 2,6-dialkyl-4-pyrones.[102–107] 2-

[86] N. V. Khromov-Borisov and L. A. Gavrilova. *Zh. Obshch. Khim.* **32**, 86 (1962).
[87] N. V. Khromov-Borisov and L. A. Gavrilova, *Zh. Obshch. Khim.* **32**, 3211 (1962).
[88] H. Strzelecka, *Ann. Chim. (Paris)* Ser. **14**, **1**, 201 (1966).
[88a] H. Strzelecka and M. Simalty, *Bull. Soc. Chim. France* p. 832 (1968).
[89] A. N. Narkevich, G. N. Dorofeenko, and Y. A. Zhdanov, *Zh. Organ. Khim.* **1**, 975 (1965).
[90] E. E. Royals and J. C. Leffingwell, *J. Org. Chem.* **30**, 1255 (1965); J. A. Berson, *J. Am. Chem. Soc.* **74**, 5172 (1952).
[91] F. Arndt, B. Eistert, H. Scholz, and E. Aron, *Ber. Deut. Chem. Ges.* **69**, 2373 (1936).
[92] F. Arndt, *Org. Synth.* Collective Vol. III, p. 231 (1955).
[93] L. C. King, F. J. Ozog, and J. Moffat, *J. Am. Chem. Soc.* **73**, 300 (1951).
[94] R. Cornubert, R. Delmas, S. Monteil, and J. Wirst, *Bull. Soc. Chim. France* p. 40 (1950).
[95] I. El-Kholy, F. K. Rafla, and G. Soliman, *J. Chem. Soc.* p. 2588 (1959).
[96] W. Borsche and W. Peter, *Ann. Chem.* **453**, 148 (1927).
[97] N. J. Leonard and J. Choudhury, *J. Am. Chem. Soc.* **79**, 156 (1957).
[98] R. Willstätter and R. Pummerer, *Ber. Deut. Chem. Ges.* **38**, 1461 (1905).
[99] A. Dornow and F. Ische, *Angew. Chem.* **67**, 653 (1955).
[100] R. Mayer, *Chem. Ber.* **90**, 2362 (1957).
[101] R. Mozingo and H. Adkins, *J. Am. Chem. Soc.* **60**, 669 (1938).
[102] S. S. Deshapande, *J. Indian Chem. Soc.* **9**, 303 (1932).
[103] J. D. von Mikusch-Buchberg and A. N. Sagredos, *Ann. Chem.* **681**, 118 (1965).
[104] A. N. Sagredos and J. D. Mikusch, *Ann. Chem.* **697**, 111 (1966).
[105] A. N. Sagredos, *Ann. Chem.* **700**, 29 (1966).
[106] A. N. Sagredos, *Ann. Chem.* **706**, 90 (1967).
[107] E. B. Mullock and H. Suschitzky, *J. Chem. Soc.* C, 828 (1967).

Pyrones which can be easily obtained are 4,6-dimethylcoumalin[108, 109] and 4,6-diphenylcoumalin.[110]

4*H*-Pyran-4-thiones (4-thiopyrones) may be obtained from 4-pyrones with phosphorus pentasulfide (e.g., cf. King *et al.*[93]) (the direct reaction of sulfur with 4-unsubstituted pyrylium salts has not yet been described, although by analogy with dithiolium salts it is plausible[111]).



(**23**) (**24**)

Electrophilic reagents become bonded to the carbonyl oxygen or sulfur atom of (thio)pyrones, leading to pyrylium salts.

Protonation converts pyrones (**23**, Y = O) into hydroxypyrylium salts (**24**, Y = O, R = H) and thiopyrones (**23**, Y = S) into mercaptopyrylium salts (**24**, Y = S, R = H).

In the hands of Collie and Tickle[35] in 1899 this reaction gave the first crystalline pyrylium salts. The salt character of the compounds was proved by conductivity measurements[112]; the basicity of 2,6-dimethylpyrone was found[112] to be a little higher than that of urea. Basicities of other pyrones decrease in the order: 2,6-dimethyl- > 2-phenyl-6-methyl- > 2,6-diphenylpyrone,[113] paralleling the dipole moments. These hydroxypyrylium salts hydrolyze in water to pyrones.[114, 115] The formation of salts of 2,6-dimethylpyrone with organic acids was investigated by Kendall,[116] and with mineral acids by Cook.[117]

[108] A. Hantzsch, *Ann. Chem.* **222**, 1 (see p. 16) (1884).
[109] I. Alkonyi, *Chem. Ber.* **98**, 3099 (1965).
[110] C. L. Bickel, *J. Am. Chem. Soc.* **72**, 1022 (1950).
[111] E. Klingsberg, *J. Org. Chem.* **28**, 529 (1963).
[112] H. N. K. Rördem, *J. Am. Chem. Soc.* **37**, 557 (1915); B. Trémillon, *Bull. Soc. Chim. France* p. 1940 (1960); A. I. Tolmachev, L. M. Shulezhko and A. A. Kisilenko, *Zh. Obshch. Khim.* **38**, 118 (1968).
[113] E. I. Johnson and J. R. Partington, *J. Chem. Soc.* p. 86 (1931).
[114] J. Walker, *Ber. Deut. Chem. Ges.* **34**, 4115 (1901).
[115] P. Walden, *Ber. Deut. Chem. Ges.* **34**, 4185 (1901).
[116] J. Kendall, *J. Am. Chem. Soc.* **36**, 1222 (1914).
[117] D. Cook, *Can. J. Chem.* **39**, 31, 1187, 2009 (1961); **40**, 2362 (1962); **41**, 505 (1963).

The *alkylation* of 2,6-dimethylpyrone was discovered by Baeyer and Villiger[37] who noted that with dimethyl sulfate a syrupy liquid is formed. Kehrmann and Duttenhöfer[38] obtained from this syrup a crystalline methiodide (**24**, Y = O, R = CH_3, X = I). These workers noted that direct formation of the methiodide from methyl iodide and 2,6-dimethylpyrone was not possible; this finding was confirmed by later workers.[118] Alkyl tosylates are also inactive,[118] but diethyl sulfate can replace dimethyl sulfate.[119, 120] From 2,6-dimethylpyrone methosulfate, a crystalline perchlorate can be obtained[22] whose conductivity was found[39] to be identical with that of 2,6-lutidinium perchlorate; this fact was interpreted as disproving formula **21**. As alkylating agents for pyrones, trialkyloxonium fluoroborates are superior to other agents[121, 122]; besides these reagents, Meerwein and co-workers also employed alkyl iodides and silver fluoroborate,[123] a procedure adopted also for alkoxypyrones.[124, 125] Dimroth and Heinrich[126] reported that dimethoxyphenylcarbonium fluoroborate immediately methylates 2,6-dimethyl-4-pyrone. From the unsubstituted 4-pyrone and dimethyl sulfate, 4-methoxypyrylium salts can be obtained in good yield.[127] Alkyl *o*-nitrobenzene sulfonates were similarly used for alkylating pyrones.[73]

Thiopyrones and selenopyrones can be alkylated more readily than pyrones. Thus 2,6-dimethyl-4*H*-pyran-4-thione (4,6-dimethyl-4-thiopyrone) (**23**, Y = S) reacts rapidly with methyl iodide yielding a 4-methylmercaptopyrylium iodide[93] (**24**, Y = S, R = Me, X = I). Many alkylating agents were investigated by King *et al.*[93] The kinetics of the reaction between 2,6-dimethyl-4-thiopyrone and substituted phenacyl bromides was found to be described by the Hammett

[118] R. M. Anker and A. H. Cook, *J. Chem. Soc.* p. 117 (1946).
[119] G. A. Reynolds (to Eastman Kodak Co.), U.S. Patent No. 3,148,067 (Sept. 8, 1964); *Chem. Abstr.* **61**, 15571 (1964).
[120] A. Szuchnik, *Roczniki Chem.* **30**, 73 (1956).
[121] H. Meerwein, G. Hinz, P. Hofmann, E. Kroning, and E. Pfeil, *J. Prakt. Chem.* **147**, 257 (1937).
[122] H. Meerwein, V. Hederich, and K. Wunderlich, *Arch. Pharm.* **291**, 541 (1958).
[123] H. Meerwein and K. Wunderlich, *Angew. Chem.* **69**, 481 (1957).
[124] P. Beak, *Tetrahedron Letters* p. 863 (1963).
[125] P. Beak, *Tetrahedron* **20**, 831 (1964).
[126] K. Dimroth and P. Heinrich, *Angew. Chem. Intern. Ed. English* **5**, 676 (1966)
[127] K. Hafner and H. Kaiser, *Ann. Chem.* **618**, 140 (1958).

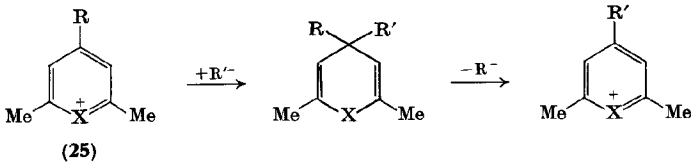
equation with $\rho = 1$.[128] The formation of other alkylmercaptopyrylium salts has been reported.[129–131] 4-Selenopyrones behave analogously yielding 4-alkylselenopyrylium salts (**24**, Y = Se, R = Alk) very easily.[132]

By *O-acylation* with 2-methyl-1,3-dioxolenium fluoroborate, which reacts as O-acetyl ethylene oxide, 2,6-dimethyl-4-pyrone is converted into 4-acetoxy-2,6-dimethylpyrylium fluoroborate[133] (**24**, Y = O, R = Ac, X = BF_4). The alleged compound with this structure which has been obtained from **8** and acetyl fluoroborate[134] is, in fact,[133] the BF_3-complex of the pyrone.

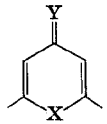
c. *Nucleophilic Displacement of (Thio)alkoxy Groups from (Thio)-alkoxypyrylium Salts.* 4-Alkoxy groups of pyrylium salts undergo nucleophilic displacement very easily, even with weak nucleophiles. On recrystallization of 2,6-dimethyl-4-methoxypyrylium perchlorate (**22**, X = ClO_4) from ethanol, the methoxy group is exchanged by ethoxy; recrystallization of the latter salt from methanol leads back to **22** (X = ClO_4).[118] Water exchanges alkoxy groups by hydroxy, and hence hydrolyzes alkoxypyrylium salts to pyrones.[22] Other nucleophilic reagents which may replace alkoxy groups are thiols such as benzylmercaptan and secondary amines such as piperidine or morpholine.[118] Hydrogen sulfide, sodium hydrosulfide, or sodium sulfide react readily with 4-alkoxypyrylium salts (**25**, X = O, R = OMe) (pyrones react much more sluggishly) leading to 4-mercaptopyrylium salts (**25**, X = O, R = SH) and hence to 4-thiopyrones (**23**, Y = S).[130] Thus, an alternative route from pyrones to thiopyrones or thiopyrylium salts is available, by intermediate alkylation which causes an enhancement of the reactivity toward nucleophiles. Likewise, sodium hydrogen selenide or sodium selenide afford selenopyrones (**23**, Y = Se).[132]

Subsequent studies by King and Ozog[135] showed that the ease with which the 4-substituent R is replaced by R′ in **25** (X = O)

[128] F. J. Ozog, V. Comte, and L. C. King, *J. Am. Chem. Soc.* **74**, 6225 (1952).
[129] A. Hantzsch, *Ber. Deut. Chem. Ges.* **52**, 1535 (1919).
[130] G. Traverso, *Ann. Chim. (Rome)* **46**, 821 (1956).
[131] R. L. Letsinger and J. D. Jamison, *J. Am. Chem. Soc.* **83**, 193 (1961).
[132] G. Traverso, *Ann. Chim. (Rome)* **47**, 1244 (1957).
[133] H. Meerwein, K. Bodenbenner, P. Borner, F. Kunert, and K. Wunderlich, *Ann. Chem.* **632**, 38 (1960).
[134] F. Seel, *Z. Anorg. Allgem. Chem.* **250**, 331 (see p. 349) (1943).
[135] L. C. King and F. J. Ozog, *J. Org. Chem.* **20**, 448 (1955).



(25)



(26)

decreases in the order R = MeO > MeS > Me_2N, i.e., in the order of increasing basicity. 4-Alkoxypyrylium salts can be converted into alkylmercapto- or dialkylaminopyrylium, and alkylmercapto- into dialkylaminopyrylium salts, but the reverse processes are not possible, e.g., 4-dialkylaminopyrylium salts do not react with alcohols or thiols. Such exchange is also possible, but with a lower rate, for pyridinium salts (**25**, X = NMe) which exchange OR or SR groups with NR_2 groups, but do not exchange OR by SR groups. With primary amines in excess, e.g., with methylamine, 4-methoxy-2,6-dimethylpyrylium perchlorate (**22**, X = ClO_4) undergoes replacement of both the alkoxy group and the heteroatom yielding 2,6-dimethyl-4-methylamino-*N*-methylpyridinium perchlorate (**25**, X = NMe, R = NHMe). Because **22** with ammonia or ammonium carbonate yields 4-methoxy-2,6-lutidine[22] by replacing only the heteroatom, it is plausible[135] that the first rapid step is the formation of a pyridinium ion, followed by slow displacement of the alkoxy group.

A similar replacement of the oxygen heteroatom by sulfur to thiapyrylium salts (**25**, X = S) can occur on treatment with Na_2S or NaSH. By making use of the difference in reactivity between OAlk and SAlk groups and of the strong complexation of RSH with mercury salts, Arndt *et al.*,[136] Traverso,[130, 132, 137] Wizinger and Ulrich,[138, 139] and Ohta and Kato[140] with their co-workers succeeded in preparing

[136] F. Arndt and N. Bekir, *Ber. Deut. Chem. Ges.* **63**, 2393 (1930); F. Arndt and C. Martius, *Rev. Fac. Sci. Univ. Istanbul* **A13**, 57 (1948); *Chem. Abstr.* **42**, 4176 (1948).

[137] G. Traverso, *Chem. Ber.* **91**, 1224 (1958) and previous papers.

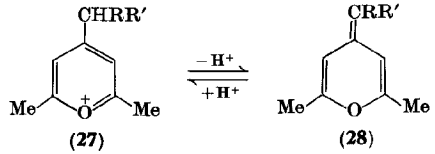
[138] R. Wizinger and P. Ulrich, *Helv. Chim. Acta* **39**, 207 (1956).

[139] R. Wizinger and P. Ulrich, *Helv. Chim. Acta* **39**, 217 (1956).

[140] M. Ohta and H. Kato, *Bull. Chem. Soc. Japan* **32**, 707 (1959).

thiopyrones (**23**, Y = S), thiapyrones (**26**, X = S, Y = O), and thiathiopyrones (**26**, X = Y = S) starting from pyrones (**26**, X = Y = O).

Ohta and Kato[140] found that in the presence of bases the OMe group of **22** may be displaced by compounds with active methylene groups (ethyl cyanoacetate, malonodinitrile), yielding **27**, which can be deprotonated to a methylenepyran derivative (**28**, R = CN, R′ = CN or CO_2Et).



(27) (28)

d. *Nucleophilic Displacements at Pyrones.* In fact, this is a particular case of the former type, since pyrones, and even more thiopyrones, behave as pyrylium oxides and mercaptides, respectively (**8b**). A separate paragraph was deemed necessary, however, owing to the historical importance of the method and to its relative importance. The above reactivity sequence for the replacement of the R group in **25** can be completed R = MeO > MeS > Me_2N > O^-; in fact, the nucleophilic displacements occur just in this order, the pyrone reacting more sluggishly and requiring more powerful nucleophiles than alkoxy, alkylmercapto, or dialkylaminopyrylium salts.

The usual carbonyl reagents (hydrazines, semicarbazone, hydroxylamine) do not give the normal derivatives, but lead to ring contraction and formation of pyrazoles or isoxazoles. However, a semicarbazone and an oxime of 2,6-diphenylpyrone has been obtained by Arndt *et al.*,[141] indirectly, through the intermediacy of the more reactive 4-thiopyrone.

Diphenylketene has been reported to react with 2,6-dimethylpyrone affording the diphenylmethylenepyran (**28**, R = R′ = Ph) after splitting off carbon dioxide.[142]

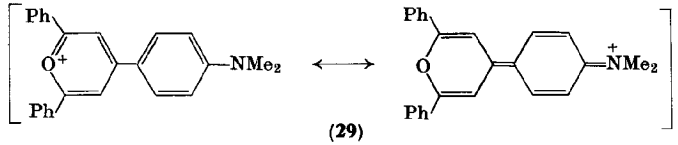
Wizinger and co-workers[143] found that 2,6-diphenyl-4-pyrone or 4,6-diphenyl-2-pyrone react with *N*,*N*-dimethylaniline in the presence of $POCl_3$ and PCl_5, yielding triarylpyrylium salts **29** and **30**, respectively. With the same condensing agents, the above authors reacted

[141] F. Arndt, G. T. O. Merlin, and J. R. Partington, *J. Chem. Soc.* p. 602 (1935).

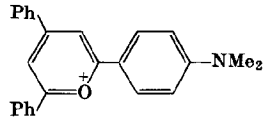
[142] H. Staudinger and N. Kon, *Ann. Chem.* **384**, 38 (see p. 129) (1911).

[143] R. Wizinger, A. Grüne, and E. Jacobi, *Helv. Chim. Acta* **39**, 1 (1956).

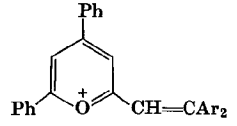
4,6-diphenyl-2-pyrone with 1,1-diarylethylenes leading to 2-styrylpyrylium salts (**31**, Ar = anisyl and/or phenyl). Even CH_2= groups of methylenepyrans (anhydro bases) can act as nucleophiles. Indeed, in the presence of tertiary bases, 4-alkoxypyrylium salts undergo autocondensation to pyrylocyanines **32**[118–120]; similarly, pyrones react with anhydro bases of 2,4,6-trialkylpyrylium salts on refluxing in acetic anhydride, affording colored symmetric (**33**) or asymmetric (**34**) pyrylocyanines[76, 77] (cf. Section II, B, 1, a).



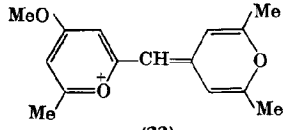
(29)



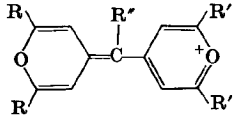
(30)



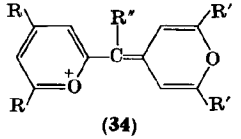
(31)



(32)



(33)



(34)

The more conventional nucleophiles obtained from compounds with active methylene groups, such as malonodinitrile or ethyl cyanoacetate give[144–147] similar methylenepyrans (**28**, R = R′ = CN

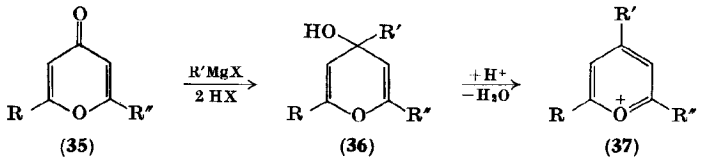
[144] L. L. Woods, *J. Am. Chem. Soc.* **80**, 1440 (1958).
[145] L. L. Woods, *J. Org. Chem.* **22**, 341 (1957).
[146] D. Fărcasiu, *Rev. Roumaine Chim.* **9**, 865 (1964).
[147] S. Yamamura, K. Kato, and Y. Hirata, *Tetrahedron Letters* p. 1637 (1967); J. A. Van Allan, G. A. Reynolds, and D. P. Maier, *J. Org. Chem.* **33**, 4418 (1968).

and/or COOEt) with 4-pyrones as with 4-alkoxypyrylium salts (the reaction is carried out in refluxing acetic anhydride, so that 4-acetoxypyrylium salts are plausible intermediates). The same reaction may be catalyzed by bases, and may be effected also with rhodamine,[140] barbituric acid derivatives (cyclic malonodiamides), pyrazolones, etc.[76, 77, 148] Nitromethane or cyclopentadiene do not react with pyrones,[148, 149] but tetrachloro- or tetramethoxycyclopentadienes afford cyclopentadienylidenepyrans.[149] Tri- and tetraphenylcyclopentadienylidenepyrans[150] and 9-fluorenylidenepyrans[151] are also known. These compounds are heteroanalogs of sesquifulvalene.[152]

The best-known reaction pertaining to this type is the condensation of pyrones with Grignard reagents. One year after Gomberg and Cone[153] had reported that they had observed no reaction between 2,6-dimethylpyrone and phenylmagnesium bromide, Baeyer and Piccard[32] reacted 2,6-dimethylpyrone with methylmagnesium iodide obtaining 2,4,6-trimethylpyrylium perchlorate (**2**),[48] and with phenylmagnesium bromide obtaining 2,6-dimethyl-4-phenylpyrylium perchlorate,[48, 68, 75] the first pyrylium salts without alkoxy substituents to be identified. Since pyrylium salts also react with organomagnesium derivatives (cf. Section II, B, 1, e), it is necessary to mix rapidly at low temperature equimolar amounts of reagents and to pour the mixture after 1–2 minutes into an excess of cold concentrated acid. The procedure is delicate and the yields moderate (30–35%); 2,6-dimethylpyrone and isopropylmagnesium bromide[76, 77] or *t*-butylmagnesium chloride[127] give pyrylium salts in 50% yield. Also, 2,6-diphenylpyrone reacts with methylmagnesium iodide normally[154]; 2,6-diphenylthiapyr-4-one reacts with methylmagnesium iodide affording 2,6-diphenyl-4-methylthiapyrylium.[139]

So far, this reaction finds application for the conversion of 4-pyrone into 4-substituted pyrylium salts with free α-positions, for which few

[148] F. Eiden, *Arch. Pharm.* **293**, 404 (1960); F. Eiden and H. Fenner, *Chem. Ber.* **101**, 3403 (1968).
[149] G. Seitz, *Angew. Chem.* **79**, 96 (1967).
[150] D. Lloyd and F. I. Wasson, *J. Chem. Soc.* C, 1086 (1966); *Chem. Ind. (London)* p. 1559 (1963).
[151] A. Schönberg, M. Elkaschef, M. Nosseir, and M. M. Sidky, *J. Am. Chem. Soc.* **80**, 6312 (1958).
[152] G. V. Boyd, *Proc. Chem. Soc.* p. 93 (1959).
[153] M. Gomberg and L. H. Cone, *Ann. Chem.* **376**, 182 (1910).
[154] H. Kling, Ph.D. Thesis, Univ. of Basel, 1950.



(35) (36) (37)

other methods exist. Köbrich[155] has prepared the hygroscopic 4-methylpyrylium perchlorate in 30% yield (**37**, R = R″ = H, R′ = Me), and Kelemen and Wizinger[77] obtained 4-phenylpyrylium in 80% yield. If for the hydrolysis of the reaction mixture dilute acid is employed, the product is not the pyrylium salt but its pseudo base.[156] The isolation of γ-pyranols (**36**) was not possible, although such pyranols are known in the chromylium (benzopyrylium) and xanthylium (dibenzopyrylium) series. A natural 2′,3′,7,6-furanobenzo-4-pyrone (khellin) also afforded benzopyrylium salts with Grignard reagents.[157]

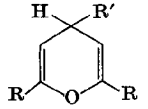
In principle, complex hydrides ($NaBH_4$, $LiAlH_4$) ought to react similarly with 4-pyrones and lead after treatment with Brønsted or Lewis acids to 4-unsubstituted pyrylium salts. This reaction has not been reported; the reduction of 2-pyrones with $LiAlH_4$ results in ring opening.[158–160]

c. *By Dehydrogenation of Pyrans.* The unsubstituted 4H-pyran remained unknown until 1962 when it was obtained independently by gas-phase pyrolysis of 2-acetoxy-3,4-dihydro-2*H*-pyran,[161] and by cyclodehydration (treatment with hydrogen chloride, then with diethylaniline) of glutardialdehyde,[162] as a colorless unstable liquid. Triphenylmethyl perchlorate in acetonitrile abstracts a hydride anion from the 4*H*-pyran prepared by the latter method, affording pyrylium perchlorate.[163] 4-Methylpyrylium perchlorate was prepared

[155] G. Köbrich, *Ann. Chem.* **648**, 114 (1961).
[156] M. A. F. Elkaschef and M. H. Nosseir, *J. Chem. Soc.* p. 4643 (1963).
[157] G. N. Dorofeenko, Y. A. Zhdanov, and T. G. Soroka, *Zh. Obshch. Khim.* **37**, 743 (1967).
[158] K. Yamada, M. Ishizaka, and Y. Hirata, *Bull. Chem. Soc. Japan*, **34**, 1873 (1961).
[159] K. Yamada, *Bull. Chem. Soc. Japan* **35**, 1329 (1962).
[160] L. R. Morgan, Jr., *J. Org. Chem.* **27**, 343 (1962).
[161] S. Masamune and H. T. Castellucci, *J. Am. Chem. Soc.* **84**, 2452 (1962).
[162] J. Strating, J. H. Keijer, E. Molenaar, and I. Brandsma, *Angew. Chem.* **74**, 465 (1962).
[163] I. Degani, R. Fochi, and C. Vincenzi, *Gazz. Chim. Ital.* **94**, 203 (1964).

similarly.[164] Hydride transfer reactions between the chromylium cation and 4*H*-pyran lead to the pyrylium cation and chroman, proving that benzopyrylium is less stable than pyrylium; similar hydride transfer reactions show that pyrylium has a stability comparable to that of selenapyrylium, but smaller than that of thiapyrylium.[165] No formation of pyrylium salts from di- or tetrahydropyrans has been reported.

A 2,4,6-trisubstituted (2*H* or 4*H*) pyran (**38**, R = R′ = Ph) was reported to result in low yield by catalytic reduction of 2,4,6-triphenylpyrylium salts[166]; by oxidation or by treatment with concentrated sulfuric acid it regenerated the triphenylpyrylium cation. There was no subsequent confirmation of this reaction. The reduction of pyrylium salts with sodium borohydride[167] affords 1,5-diones by way of 4*H*-pyrans and 2,4-dien-1-ones by way of 2*H*-pyrans.[168]



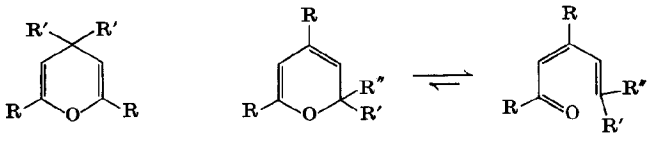
(**38**)

A convenient method leading to pyrans (**38**) consists in the nucleophilic addition of R′ anions to 2,6-disubstituted pyrylium salts, in which the γ-position (secondary carbonium ion) is more reactive than the α-positions (tertiary carbonium ions), in opposition to the reactivity of 2,4,6-trisubstituted pyrylium salts.[168a] Kröhnke and Dickoré[169] as well as Dimroth and Wolf[170] showed that 2,6-diphenylpyrylium salts add the anions R′ of nitromethane, 1,3-diketones, malonodinitrile, ethyl cyanoacetate, and benzoylacetonitrile. Similar reactions are known in the flavylium series.[169, 171] Nonactivated R′

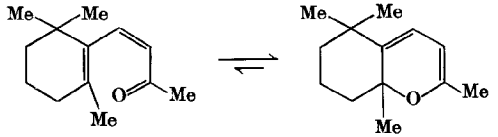
[164] I. Degani and C. Vincenzi, *Boll. Sci. Fac. Chim. Ind. Bologna* **25**, 51 (1967).
[165] I. Degani, R. Fochi and C. Vincenzi, *Boll. Sci. Fac. Chim. Ind. Bologna* **23**, 21 (1965).
[166] W. Dilthey, *J. Prakt. Chem.* **101**, 177 (1921).
[167] A. T. Balaban, G. Mihai, and C. D. Nenitzescu, *Tetrahedron* **18**, 257 (1962).
[168] T. A. Gosinck, Ph.D. Thesis, Oregon State Univ., 1966; *Dissertation Abstr.* **27**, 3852 (1967).
[168a] A steric factor could also favor 4-additions over 2-additions in 2,6-disubstituted pyrylium salts.
[169] F. Kröhnke and K. Dickoré, *Chem. Ber.* **92**, 46 (1959).
[170] K. Dimroth and K. H. Wolf, *Angew. Chem.* **72**, 777 (1960).
[171] R. L. Shriner and R. Sutton, *J. Am. Chem. Soc.* **85**, 3989 (1963).

groups may be introduced into the 4-position of 2,6-disubstituted pyrylium salts by reaction with R'MgX, e.g., R' = Me, iso-Pr, $PhCH_2$, *t*-Bu, Ph, etc.[170]

The pyran **38** is decomposed by acids into the initial reagents, 2,6-disubstituted pyrylium salt and R^- anion, when the latter anion is resonance-stabilized, but into a new 2,4,6-trisubstituted pyrylium salt and hydride ion (which is transferred to an acceptor) in the case of **38** (R' = Alk or Ar). The acceptor can be methylene blue or indigo,[169] but with strong acids ($HClO_4$, HBF_4, or $FeCl_3$ + AcOH) no added acceptor is necessary; some of the pyran is probably reduced. From 2,6-diphenylpyrylium perchlorate one can thus prepare 2,6-diphenyl-4-alkyl or -aryl pyrylium salts in yields up to 70%.[170] If pyrans (**38**, R' = CHRR') are dehydrogenated in neutral or alkaline medium (with $KMnO_4$ in cold dimethylformamide,[169] or with alkaline ferricyanide in the presence of 2,4,6-triphenylphenol as hydride carrier[170]),



(39) (40a) (40b)



(41a) (41b)

then the anhydro base **28** is obtained in 65–85% yield. The pyran (**38**, R = Ph, R' = CH_2COPh) dehydrogenates spontaneously on recrystallization from ethyl acetate;[169] the resulting compounds (**28**) are identical with those obtained from pyrones and compounds with active methylene groups (Section II, B, 1, c). A related compound (**28**, all substituents being aryl groups) was formed from 2,6-diarylpyrones (aryl = anisyl and/or phenyl) and diphenyldiazomethane.[156] Triphenylmethyl perchlorate can also dehydrogenate pyrans **38**.[171a]

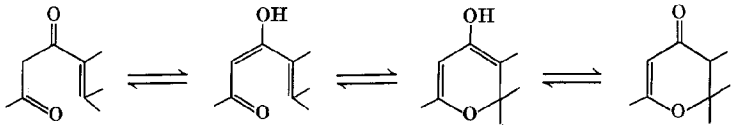
Pyrans like **39** or **40a, b**, which are formed from organomagnesium or organolithium reagents and 2,4,6-trisubstituted pyrylium salts,[172–180a] 4-pyrones,[182,183] or 2-pyrones,[182–188] by aldol condensation of ketones,[189,190] by dehydration of 1,5-diones in the case of **39** (R = R' = Ph),[191,192] or in the case of **41** by photochemical conversion of *trans*-β-ionone,[193] cannot be converted into pyrylium salts because they have no removable hydrogen atoms. 2*H*-Pyrans present, however, an interesting valence tautomerism between pyran and dienone forms.[168,194,194a] In the equilibrium mixture of **41a, b**, the pyran form **41b** prevails at room temperature over the *cis*-β-ionone (**41a**), but at 112° the two forms are in almost equal concentration in the equilibrium mixture. The *cis*-dienonic form (**40b**) seems to be, however, the more stable isomer in the system (**40a, b**, R = R' = CH_3, R'' = H). It appears that simple *cis*-pentadienals and *cis*-pentadienones are more stable than their α-pyran valence isomers, and that substitution by phenyl

[171a] S. V. Krivun, *Dokl. Akad. Nauk SSSR*, **182**, 347 (1968).

[172] G. Köbrich, *Angew. Chem.* **72**, 348 (1960).
[173] G. Köbrich and D. Wunder, *Ann. Chem.* **654**, 131 (1962).
[174] G. Köbrich and W. E. Breckoff, *Ann. Chem.* **704**, 42 (1967).
[175] J. Royer and J. Dreux, *Compt. Rend.* **258**, 5895 (1964).
[176] J. Royer and J. Dreux, *Compt. Rend.* **C262**, 927 (1966); C. Decoret and J. Royer, *Compt. Rend.* **267**, 1614 (1968).
[177] K. Dimroth and G. Neubauer, *Chem. Ber.* **92**, 2042 (1959).
[178] K. Dimroth and K. H. Wolf, *Angew. Chem.* **72**, 778 (1960).
[179] K. Dimroth, K. Wolf, and H. Kroke, *Ann. Chem.* **678**, 183 (1964).
[180] K. Dimroth, H. Kroke, and K. Wolf, *Ann. Chem.* **678**, 202 (1964).
[180a] The pyrylium ring is an ambident cation (see ref. 181) reacting at the α- (as **1b**) or γ-positions (as **1c**).
[181] S. Hünig, *Angew. Chem.* **76**, 400 (1964).
[182] R. Gompper and O. Christmann, *Angew. Chem.* **71**, 32, 378 (1959).
[183] R. Gompper and O. Christmann, *Chem. Ber.* **94**, 1795 (1961).
[184] R. Gompper and O. Christmann, *Chem. Ber.* **94**, 1784 (1961).
[185] J. P. Schirmann and J. Dreux, *Compt. Rend.* **C262**, 652 (1966); *Bull. Soc. Chim. France* p. 3896 (1967).
[186] P. Rouiller, D. Gagnaire, and J. Dreux, *Bull. Soc. Chim. France* p. 689 (1966).
[187] J. P. Montillier and J. Dreux, *Bull. Soc. Chim. France* p. 4025 (1967).
[188] P. Rouiller and J. Dreux, *Compt. Rend.* **258**, 5228 (1964).
[189] A. Hinnen and J. Dreux, *Compt. Rend.* **255**, 1747 (1962).
[190] A. Hinnen and J. Dreux, *Bull. Soc. Chim. France* p. 1492 (1964).
[191] A. Peres de Carvalho, *Compt. Rend.* **199**, 1430 (1934).
[192] A. Peres de Carvalho, *Ann. Chim. (Paris)* **4**, 486 (1935).
[193] G. Büchi and N. C. Yang, *Helv. Chim. Acta* **38**, 1338 (1955).
[194] E. N. Marvell, G. Caple, T. A. Gosinck, and G. Zimmer, *J. Am. Chem. Soc.* **88**, 619 (1966).
[194a] P. Schiess, H. L. Chia, and C. Suter, *Tetrahedron Letters*, p. 5747 (1968); P. Schiess and C. Suter, *Chimia (Aarau)* **22**, 483 (1968).

groups or the presence of fused saturated rings shifts the equilibrium in favor of the pyran.[168,195] This valence isomerization, which is a concerted process with a 6-membered transition state,[196] has a fairly low activation energy, and may be termed valence tautomerism.

The equilibrium between 2,3-dihydro-4-pyrones and 1-penten-3,5-diones[197] is a related process which can be pictured as involving a reaction with a cyclic 6-membered transition state (see Scheme 2).

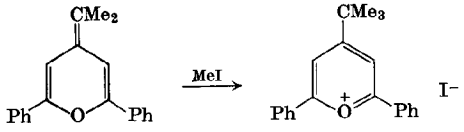


SCHEME 2.

Despite the increasing information on the photochemistry of 2,4-dienones[198] and other unsaturated ketones,[199] as well as on the ring-chain valence isomerism of halogen-substituted pyran and dihydropyran systems,[200–201] the data are still very scarce. The intermediate formation of pyrans valence-isomeric with unsaturated carbonyl compounds in the pyridine syntheses based on reactions of ammonia with aldehydes or ketones, advocated by various authors[202–205] (cf. Section II,B,2,f), is still rather speculative. (See also Section II,B,2,e for the valence isomerism of 5-chloro-2,4-dienones with pyrylium chlorides.)

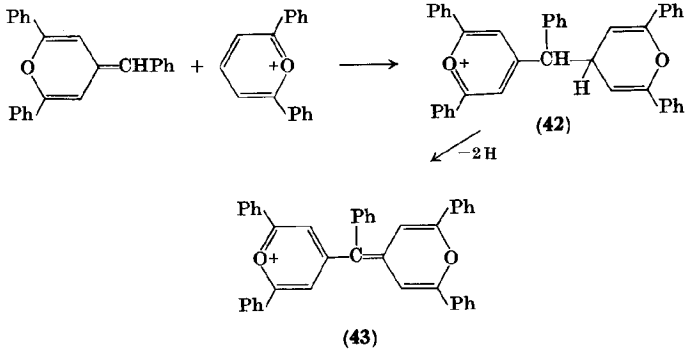
195 E. N. Marvell and P. Churchley, *Am. Chem. Soc., 144th Meeting, Los Angeles, Calif., March–April 1963* Abstr. of Papers, p. 47M.
196 A. T. Balaban, *Rev. Roumaine Chim.* **11**, 1097 (1966); **12**, 875 (1967).
197 S. Gelin and R. Gelin, *Compt. Rend.* **C264**, 1858 (1967); *Bull. Soc. Chim France* p. 288 (1968).
198 P. De Mayo and S. T. Reid, *Quart. Rev. (London)* **15**, 393 (1961); R. Becker and J. Michl, *J. Am. Chem. Soc.* **88**, 5931 (1966); V. P. Dzyuk V. F. Lavrushin, and V. N. Tolmachev, *Zh. Obshch. Khim.* **36**, 336 (1966)
199 J. M. Conia and P. LePerchec, *Bull. Soc. Chim. France* p. 273, 278, 281, 28[illegible] (1966).
R. A. Schneider and J. Meinwald, *J. Am. Chem. Soc.* **89**, 2023 (1967).
200 S. Sarel and J. Rivlin, *Tetrahedron Letters* p. 821 (1965).
201 J. C. Anderson, D. G. Lindsay, and C. B. Reese, *Tetrahedron* **20**, 2091 (1964).
202 S. M. Sherlin, A. Y. Berlin, T. A. Serebrennikova, and F. L. Rabinovich, *Zh. Obshch. Khim.* **8**, 22 (1938).
203 K. Alder, H. Ofermans and E. Rüden, *Ber. Deut. Chem. Ges.* **74**, 905 (1941).
204 J. Herzenberg and G. Boccato, *Chim. Ind. (Paris)* **80**, 248 (1958).
205 J. Gelas, *Bull. Soc. Chim. France* p. 3093 (1967).

f. *Electrophilic Reactions of Methylenepyrans.* Methylenepyrans or anhydro bases of pyrylium salts with alkyl groups in positions 2, 4, or 6 possessing benzylic hydrogens, are relatively stable when they have electronegative substituents at the exocyclic carbon atom, like nitro, acyl, or cyano groups. On protonation they yield pyrylium salts, e.g., **27**. The preparation of such methylenepyrans was described in Section II,B,1,d; two more examples follow. The dimer of 1,3-dibenzoylallene has a structure related to **10**; its reversible protonation to a pyrylium salt of type **11** (R = Ph) constituted a proof of its structure.[206] Dichlorocarbene reacts with 4*H*-pyran affording chloromethylenepyran.[207] For further examples, cf. Sections II,C,2,f and D,1,a.



SCHEME 3.

Such methyenepyrans afford still another possibility for obtaining new pyrylium salts, namely, electrophilic alkylation or acylation at the exocyclic methylene carbon atom. Thus, 2,6-diphenyl-4-isopropylidene-4*H*-pyran is converted into 2,6-diphenyl-4-*t*-butylpyrylium iodide on refluxing with methyl iodide[208] (see Scheme 3). Unlike the protonation of methylenepyrans, this reaction is no longer



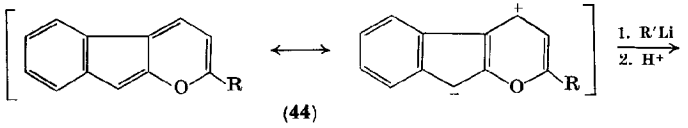
(42)

(43)

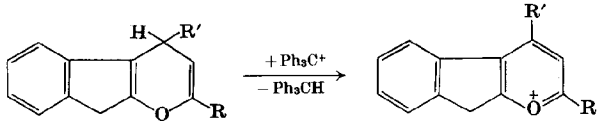
206 W. C. Agosta, *Tetrahedron* **22**, 1195 (1966).
207 K. Dimroth, W. Kinzelbach, and M. Soyka, *Chem. Ber.* **99**, 2351 (1966).
208 W. Krafft, Ph.D. Thesis, Univ. of Marburg, 1961.

reversible. The latter salt may be obtained from 2,6-diphenylpyrylium and *t*-butylmagnesium chloride, followed by dehydrogenation. The electrophilic reagent may be a pyrylium salt; the resulting pyran (**42**) dehydrogenates spontaneously (chloranil raises the yield to 75%) to the pyrylocyanine (**43**).[170]

Indenopyrans (**45**) which can be obtained after Schroth and Fischer[209] from benzoxalenes (**44**) and lithium alkyls or aryls, are γ-pyrans, and may be dehydrogenated by triphenylmethyl perchlorate to the indenopyrylium perchlorate (**46**).[210]



(44)



(45) (46)

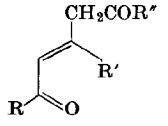
2. *From Open-Chain n-Pentene Derivatives*

Two main groups of reactions are involved: without dehydrogenation (Sections II, B, 2, a–B, 2, d) and with dehydrogenation (Sections II, B, 2, e and B, 2, f).

a. *From 2-Pentene-1,5-diones. cis*-1,5-Enediones, i.e., unsaturated δ-dialdehydes or δ-diketones (**20**) are, in fact, pseudo bases of pyrylium salts, and are formed from these salts in alkaline aqueous solution. Under the action of strong acids, they are converted back into pyrylium salts. The exchange of the oxygen heteroatom between 2,4,6-trimethylpyrylium and oxygen-18 enriched water[211] undoubtedly proceeds via this reversible ring-opening to the pseudo base (like the β-deuteration described in Section B, 1, a). Aromatic pseudo bases like those obtained from 2,4,6-triphenylpyrylium (**3**), i.e., **19** $\rightleftharpoons$ **20** (R = R′ = R″ = Ph),[34, 46] are stable crystalline compounds. This pseudo base, which according to IR and UV spectral evidence is

[209] W. Schroth and G. Fischer, *Z. Chem.* **4**, 27 (1964).
[210] W. Schroth and G. Fischer, unpublished observations, 1964.
[211] E. Gârd, A. Runge, A. Barabas, and A. T. Balaban, *J. Labelled Comds.* **3**, 151 (1967).

1,3,5-triphenyl-2-penten-1,5-dione,[212] structure confirmed by the NMR spectrum,[212a] had been obtained by Delacre and named by him "pseudodypnopinacone,"[213] then "merodypnopinancone."[214] The constitution of Delacre's product was proved by Ivanov and Ivanov[215] (cf. also Meerwein[216] and Ziegler and Schredt[217] and Section II, B, 2, f). In some cases, e.g., with 2,3,4,6-[218] and 2,3,5,6-tetraphenylpyrylium,[219] two isomers of such 1,5-enediones were isolated. On the basis of physical properties, such as UV and IR spectra,[220, 221] as well as NMR spectra,[221] the isomers differ in the *cis–trans* configuration of the C=C double bond. The isomer obtained from the pyrylium salt regenerates it rapidly with acids and is the *cis*-isomer; the other isomer, obtained from the *cis*-isomer by refluxing in benzene[219] or by the action of hot alkali,[218] is converted slowly by acids into the pyrylium salt and is the *trans*-isomer. The *cis*-isomer is sometimes the diketone (**20**) and sometimes a ketoenol (**19**); the *trans*-isomer is always a diketone (**47**).[218, 220]



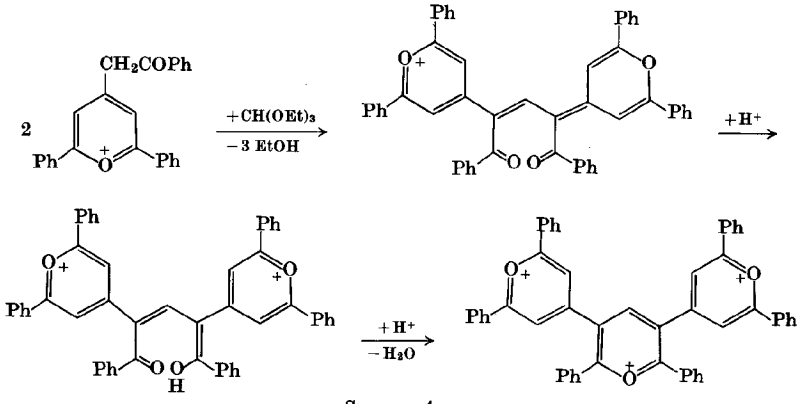
(47)

Aliphatic pseudo bases, e.g., **19** $\rightleftharpoons$ **20** (R = R′ = R″ = Me), are much less stable; they are colorless water-soluble liquids which resinify rapidly in the air. For their preparation, barium carbonate can be replaced by sodium carbonate, sodium hydrogen carbonate, or sodium acetate.[32, 39] Alkyl–aryl derivatives are also unstable, because in these cases anhydro bases are also formed and the possibilities for aldol condensations or polymerizations are greatly increased.

[212] J. A. Berson, *J. Am. Chem. Soc.* **74**, 358 (1952).
[212a] A. T. Balaban, M. Elian, D. Fărcasiu, and C. Toma, to be published.
[213] M. Delacre, *Bull. Acad. Roy. Belg. Ser. 3* **12**, 476, 501 (1891).
[214] M. Delacre, *Ann. Chim. (Paris), Ser.* 9 **2**, 90 (1914).
[215] D. Ivanov and C. Ivanov, *Ber. Deut. Chem. Ges.* **77**, 173, 180 (1944).
[216] H. Meerwein, *Ber. Deut. Chem. Ges.* **77**, 227 (1944).
[217] E. Ziegler and H. Schredt, *Monatsh. Chem.* **85**, 1191 (1954).
[218] W. Dilthey and T. Böttler, *Ber. Deut. Chem. Ges.* **52**, 2040 (1919).
[219] J. J. Basselier, *Ann. Chim. (Paris)* **6**, 1131 (1961).
[220] J. J. Basselier, *Compt. Rend.* **248**, 700 (1959).
[221] G. Rio and Y. Fellion, *Tetrahedron Letters* p. 1213 (1962).

Since 1,5-enediones are usually obtained via pyrylium salts, syntheses of the type found in Section B, 2, a have a rather theroetical interest, save for a few special syntheses. There exist several direct syntheses of 1,5-enediones, e.g., from β-chlorovinyl ketones and β-diketones or β-keto esters[222, 223]; special pathways to 1,5-enediones have also been described, namely, oxidation with lead tetraacetate or with periodic acid of cyclopentene-1,2-diols.[219, 220, 224]

The pyrylocyanine obtained by Strzelecka and Simalty from 2,6-diphenyl-4-phenacylpyrylium and orthoformic ester (cf. Section II, B, 1, a) has the structure of a pseudo base. Accordingly, its protonation is accompanied by dehydration leading to a triple pyrylium cation[88a] (see Scheme 4).

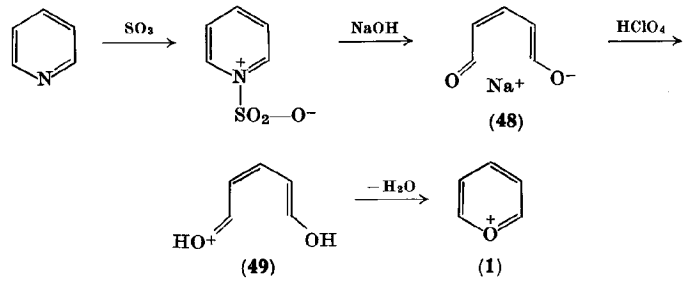


SCHEME 4.

Direct conversion of pyridines into pyrylium salts is not possible (the reverse reaction is, however, very easy). However, Klages and Träger[225] succeeded in performing the first synthesis of the parent compound **1** by the following reaction sequence, which was recently repeated with the pentadeutero derivative.[226]

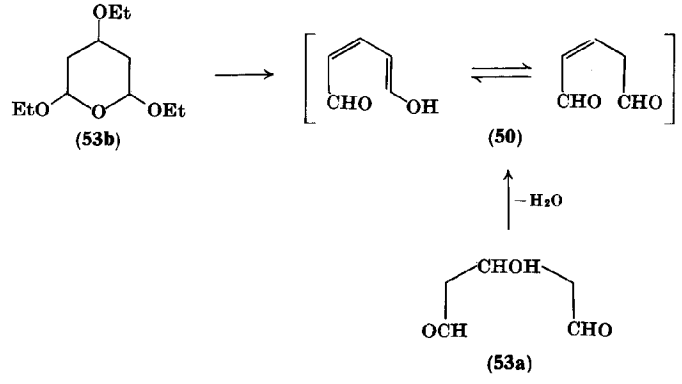
The stable sodium glutaconaldehyde enolate **48** may be recrystallized from methanol and conserved, but glutaconaldehyde (**50**) itself is extraordinarily unstable; therefore, the enolate (**48**) is directly

[222] N. K. Kochetkov and B. P. Gottich, *Zh. Obshch. Khim.* **30**, 948 (1960).
[223] V. F. Belyaev and R. I. Kozlyak, *Zh. Organ. Khim.* **3**, 1309 (1967).
[224] T. A. Geissman and C. F. Koelsch, *J. Org. Chem.* **3**, 489 (1939).
[225] F. Klages and H. Träger, *Chem. Ber.* **86**, 1327 (1953).
[226] I. I. Stănoiu and A. T. Balaban, *Rev. Roumaine Chim.* **13**, 127 (1968).

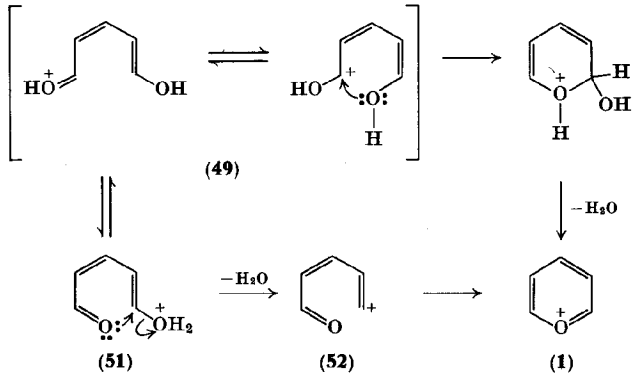


treated with concentrated perchloric acid in methanol–ether. One may prefer the protonation and dehydration of glutaconaldehyde to involve the symmetrical mesomeric intermediate **49**,[225] rather than the carbonium ion **52** (after Simalty-Siemiatycki and Fugnitto).[227] More plausible, however, is an elimination following, not preceding, the valence-isomeric ring closure of the dienone, thus avoiding cations **52**, **56b**, or **64** (cf. arrows in **51**).

The preparation of β-hydroxyglutaraldehyde (**53a**)[228] and the bisacetal (**53b**)[229] have been recently reported. Being more stable than glutaconaldehyde (**50**), they could perhaps be employed in the preparation of **1**.

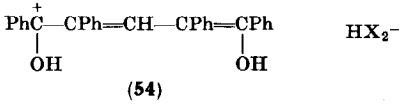


[227] M. Siemiatycki and R. Fugnitto, *Bull. Soc. Chim. France* p. 538 (1961).
[228] B. Franck and M. Schiebel, *Naturwissenschaften* **48**, 717 (1961).
[229] L. A. Yanovskaya and V. F. Kucherov, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk* p. 2097 (1964).



The interesting observation[219,230] that 1,5-enediones afford two kinds of salts has not yet been clarified. 1,2,4,5-Tetraphenyl-2-penten-1,5-dione gives with all acids whose strength is equal to or higher than that of oxalic acid, 2,3,5,6-tetraphenylpyrylium salts (dione + HX − H_2O). This is the only salt formed by perchloric acid; however, hydrogen halides and sulfonic acids are able to form one more salt (dione + 2 HX)[231] which by elimination of 1 mole of acid and 1 mole of water gives the pyrylium salt; this elimination is reversible. Water may be eliminated without acid, when hygroscopic salts (dione + 2 HX − H_2O) may be obtained.[232] The original assumption[230] that the color of pyrylium salts could be due to mesomeric cations of type **49** was disproved because salts (dione + HX) were not isolated, but it is possible that such cations exist in the hydrated salts (dione + 2 HX) (**54**).

An original method for removing mineral acids in kinetic studies or solvolyses was proposed, relying on the protonation of pseudo bases

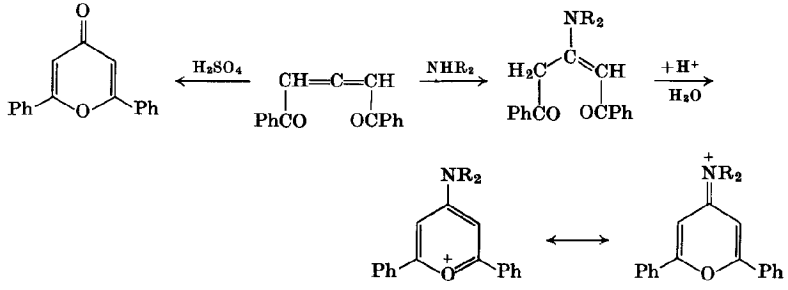


(54)

[230] C. Dufraisse, G. Rio, Y. Fellion, and J. J. Basselier, *Compt. Rend.* **252**, 32 (1961).
[231] Y. Fellion, *Compt. Rend.* **252**, 2898 (1961).
[232] Y. Fellion, *Compt. Rend.* **253**, 2078 (1961).

to pyrylium salts.[233] Pyrones were not so effective,[234] because their conjugate acids (hydroxypyrylium salts) are fairly strong acids.

The cyclization of 1,3,5-triketones to pyrones[235] will not be discussed here, although this is a related reaction, because pyrones are not true pyrylium salts. Mention will be made, however, of the formation of 2,6-diphenyl-4-pyrone from 1,3-dibenzoylallene; this ketone adds secondary amines leading to 3-dialkylamino-1,5-diphenyl-4-penten-1,5-diones, which are cyclized by hydrogen chloride in acetic acid to 2,6-diphenyl-4-dialkylaminopyrylium chlorides (R = Me and/or Ph)[236] (see Scheme 5).

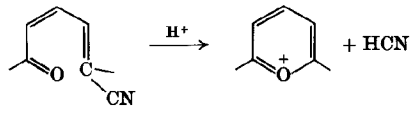


SCHEME 5.

b. *From cis-5-Cyano-2,4-pentadiene-1-ones.* A related formation of pyrylium salts can occur when the hydroxy group in pseudo bases (**19**) is replaced by another anion, e.g., CN. Pyrylium salts afford with cyanides *cis*-5-cyano-2,4-dien-1-ones (**55**)[237] which on treatment with perchloric acid regenerate the initial pyrylium salt and split off hydrogen cyanide.[238] The *trans*-isomers which are formed from the *cis*-cyanodienones by brief treatment with hydrochloric acid are no longer able to undergo cyclization.

Since 5-cyanodien-1-ones are difficultly accessible other than starting from pyrylium salts, this method has a theoretical rather than practical interest.

[233] C. Georgoulis, J. Landais, C. Prévost, and M. Siemiatycki, *Compt. Rend.* **250**, 3168 (1960).
[234] C. Prévost and C. Georgoulis, *Compt. Rend.* **250**, 1483 (1960).
[235] R. J. Light and C. R. Hauser, *J. Org. Chem.* **25**, 538 (1960); E. M. Kaiser, S. D. Work, J. F. Wolfe, and C. R. Hauser, *J. Org. Chem.* **32**, 1483 (1967).
[236] R. Bardone-Gaudemar, *Ann. Chim. (Paris)* **3**, 52 (1958).
[237] A. T. Balaban and G. D. Nenitzescu, *J. Chem. Soc.* p. 3566 (1961).
[238] A. T. Balaban, unpublished observations, 1960.



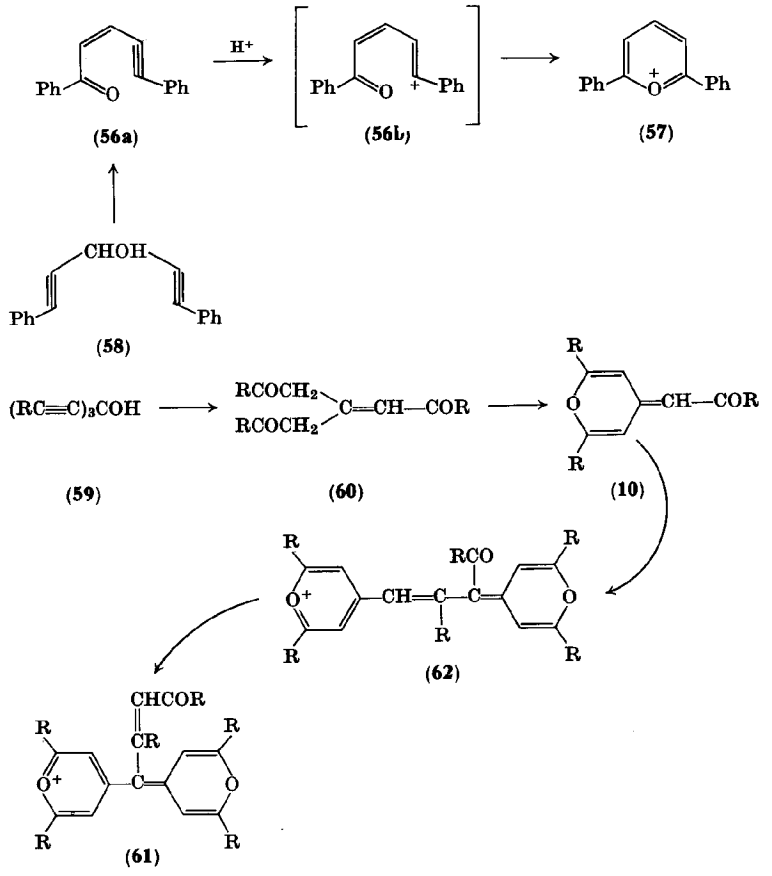
(55)

c. *From* 1-*Pentyn*-3-*en*-5-*ones*. Also related to the type found in Section B,2,a are the following two types, in which one or two $-CH_2COR$ groups in the 1,5-diones (**20**) are replaced by $-C\equiv CR$ groups. As is well known, hydration of acetylenes affords carbonyl compounds, therefore, these groups are equivalent.

Stetter and Reischl[239] described the preparation of 2,6-diphenylpyrylium perchlorate (**57**) from 1,5-diphenyl-2-penten-4-yn-1-one (**56a**) and concentrated sulfuric acid in the cold, followed by perchloric acid, in 60% yield. The process may involve hydration to a 1,5-enedione, or an ion **56b** related to **52**, and valence tautomerism.

d. *From Diethynyl Carbinols*. Starting from the observation[240] that a red dye is formed from tripropynyl carbinol (**59**, R = Me) on boiling with acetic or sulfuric acid, Simalty-Siemiatycki undertook[241–244] the study of this coloring matter (it was known[245] that diethynyl carbinols are decomposed under these conditions, but the reaction products had not been identified). From diphenylethynyl carbinol (**58**) he isolated in low yield 2,6-diphenylpyrylium (**57**), along with pyrylocyanines. The process may involve a Meyer–Schuster rearrangement[246] of **58** into **56a**, or hydrations and dehydrations. Triethynylcarbinols (**59**) give rise to pyrylocyanines; from triphenethynyl carbinol (**59**, R = Ph) the cyanine (**61**, R = Ph) was isolated and identified. An isomeric cyanine, for which formula **62** was proposed, was also isolated.[247] The process is depicted as involving the formation of a vinylogous pyrone (**10**) which can afford directly **62**, and by rearrangement **61**. Such vinylogous pyrones (**10**) have been

239 H. Stetter and A. Reischl, *Chem. Ber.* **93**, 1253 (1960).
240 C. Prévost, *Compt. Rend.* **195**, 1082 (1932).
241 M. Siemiatycki, *Compt. Rend.* **231**, 154, 359 (1950).
242 M. Siemiatycki, *Compt. Rend.* **241**, 63 (1955).
243 M. Siemiatycki, *Compt. Rend.* **242**, 3088 (1956).
244 M. Siemiatycki, *Compt. Rend.* **243**, 69, 856 (1956).
245 C. K. Liang, *Bull. Soc. Chim. France* **53**, 33 (see p. 37) (1933).
246 H. Krauch and W. Kunz, "Namenreaktionen der Organischen Chemie," 2nd Ed. Hüthig Verlag, Heidelberg, 1961.
247 M. Siemiatycki, *Ann. Chim. (Paris)* **2**, 189 (1957).

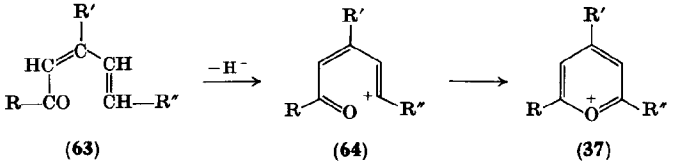


prepared with R = Ph by means of phenacylidene-triphenylphosphoranes,[88,248] (Section D,1,a) or with R = Me by triacylation of isobutene[249] (Section II,D,3,a).

e. *By Dehydrogenation of* 2,4-*Pentadien*-1-*ones*. Dilthey[250] has shown that cinnamylidene-acetophenone (**63**, R = R″ = Ph, R′ = H)

248 H. Strzelecka, M. Simalty-Siemiatycki, and C. Prévost, *Compt. Rend.* **257**, 926 (1963).
249 A. T. Balaban, P. T. Frangopol, A. R. Katritzky, and C. D. Nenitzescu, *J. Chem. Soc.* p. 3889 (1962).
250 W. Dilthey, *Ber. Deut. Chem. Ges.* **50**, 1008 (1917).

undergoes dehydrogenation and cyclization on refluxing with ferric chloride hexahydrate in acetic anhydride–acetic acid, giving 2,6-diphenylpyrylium chloroferrate in 20% yield. Antimony pentachloride may replace ferric chloride; the dienone–$SbCl_5$ adduct yields the pyrylium salt on boiling in acetic anhydride.[250] The yield was improved to 45% by changing the reactions conditions.[251] Valence isomerism between **63** and an α-pyran is probable.



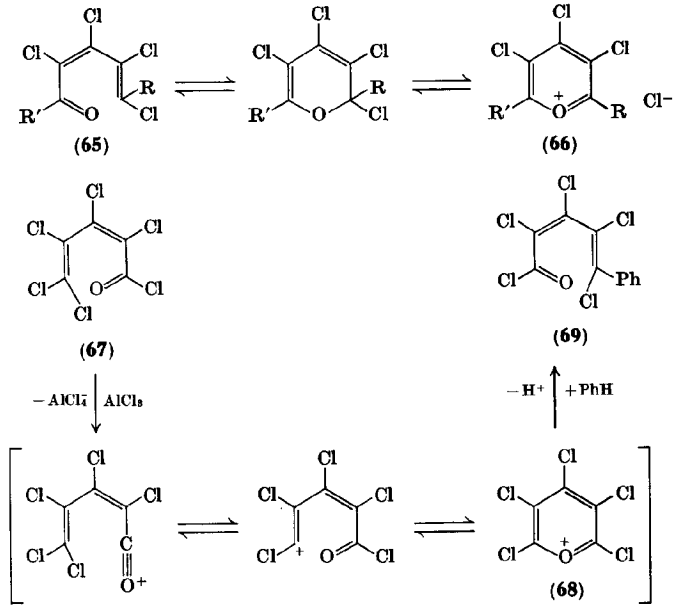
(63) **(64)** **(37)**

This method is convenient for preparing 4-unsubstituted pyrylium salts like 2,6-diphenylpyrylium. Similar ring closures were effected with cinnamylidene-benzalacetone (**63**, R = PhCH = CH, R′ = H, R″ = Ph) which gave 2 - styryl - 6 - phenylpyrylium.[250] Simalty - Siemiatycki and Fugnitto[227] showed that triphenylmethyl perchlorate can achieve the same conversion in moderate yield, and postulated a mechanism involving a cation (**64**) analogous to **52** and **56b**; details are discussed in Section II, B, 2, f (cf. also Section II, C, 2, g). Such a cation can be formed not only by hydride abstraction, but also by ionization of a chlorine anion from activated unsaturated chlorides. Roedig and Märkl found that perchloro-2,4-pentadien-1-al (**65**, R = Cl, R′ = H) gives rearrangements[252–254] and that perchloro-1,3-butadiene-5-carbonyl chloride (**67**) gives Friedel–Crafts reactions,[255, 256] both of which can best be explained by assuming the intermediate formation of tetra-(**66**, R = Cl, R′ = H) or pentachloropyrylium chloroaluminate (**68**).

Indeed, on heating with stannic, ferric, or antimonic chlorides in carbon disulfide, compounds **65** (R = H, Cl, or Ph; R′ = H or Ph) afforded crystalline pyrylium salts (**66**) with an easily hydrolyzable

[251] K. H. Wolf, Ph.D. Thesis. Univ. of Marburg, 1961.
[252] A. Roedig and G. Märkl, *Ann. Chem.* **659**, 1 (1962).
[253] A. Roedig, R. Kohlhaupt, and G. Märkl, *Chem. Ber.* **99**, 698 (1966).
[254] A. Roedig, G. Märkl, F. Frank, R. Kohlhaupt, and M. Schlosser, *Chem. Ber.* **100**, 2730 (1967).
[255] A. Roedig and G. Märkl, *Angew. Chem.* **73**, 544 (1961).
[256] A. Roedig, G. Märkl, and V. Schaal, *Chem. Ber.* **95**, 2844 (1962).

α-chloro substituent.[257] The scarce data as to the possible valence isomerism between 5 - chloro - 2,4 - pentadien - 1 - ones, 2 - chloro - 2*H*-pyrans, and pyrylium chlorides do not allow unambiguous conclusions (cf. Section B, 1, e).

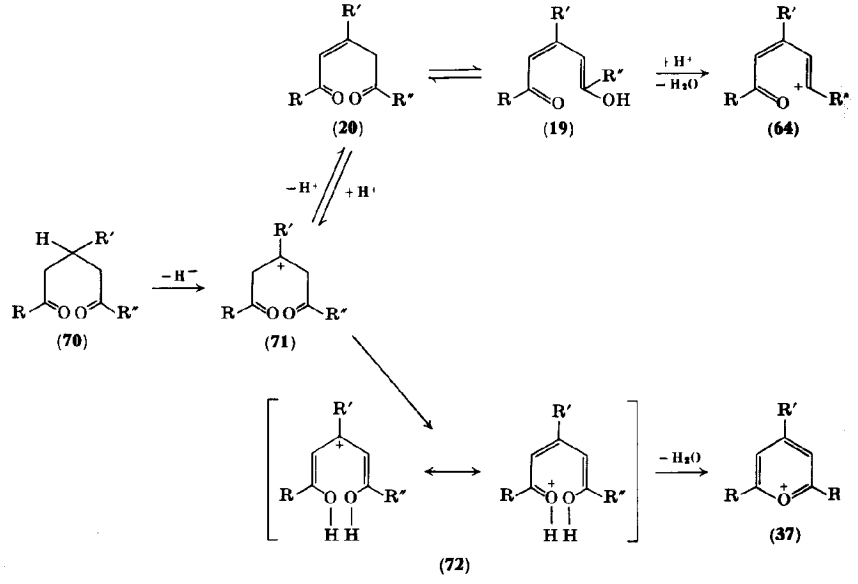


(65) **(66)** **(67)** **(69)** **(68)**

Still another possibility of isomerization is illustrated by the easy interconversions between pentaphenylpentadienoic acid chloride and 2-chloropentaphenyl-3-cyclopenten-1-one.[258] Interestingly, 2,4,6-trimethylpyrylium iodide may be sublimed without decomposition in a vacuum, possibly as a covalent 6-iodo-4-methyl-3,5-heptadien-2-one or 2-iodo-2,4,6-trimethyl-2*H*-pyran valence isomer.[259] In a related case, chlorocyclopropenes are covalent and are converted into cyclopropenium derivatives only by the action of Friedel–Crafts catalysts (electron-deficient metallic chlorides)[260] (cf. also Section II, C, 2, c.)

[257] A. Roedig, M. Schlosser, and H. A. Renk, *Angew. Chem.* **78**, 448 (1966).
[258] C. Dufraisse, G. Rio, and A. Ranjon, *Compt. Rend.* **253**, 2441 (1961); **256**, 2967 (1963); G. Rio and A. Ranjon, *Compt. Rend.* **259**, 4061 (1964).
[259] A. T. Balaban, M. Mocanu, and Z. Simon, *Tetrahedron* **20**, 119 (1964).
[260] R. Breslow, J. T. Groves, and G. Ryan, *J. Am. Chem. Soc.* **89**, 5048 (1967); S. W. Tobey and R. West, *J. Am. Chem. Soc.* **86**, 1459 (1964).

f. *By Dehydrogenation of* 1,5-*Pentanediones.* Just as the type in Section II,B,2,e corresponds to the type in Section II,B,2,c, the type in Section II,B,2,f corresponds to the type in Section II,B,2,a. Indeed, saturated 1,5-pentanediones are able to be dehydrogenated to pyrylium salts by heating with ferric chloride in acetic anhydride, as shown by Dilthey.[34,46] It was mentioned in Section I,C that von Kostanecki and Rossbach[33] had observed that benzylidene-diacetophenone (**70**, R = R′ = R″ = Ph) gave fluoroscent solutions [due to triphenylpyrylium (**3**)] in concentrated sulfuric acid, which acts as oxidant; it is much poorer than $FeCl_3 + Ac_2O$, however. Other oxidants which can act similarly are chromic anhydride or sodium persulfate in acetic anhydride, but only at higher temperatures; hydrogen peroxide, lead or manganese dioxide cannot perform this dehydrogenation.[34]

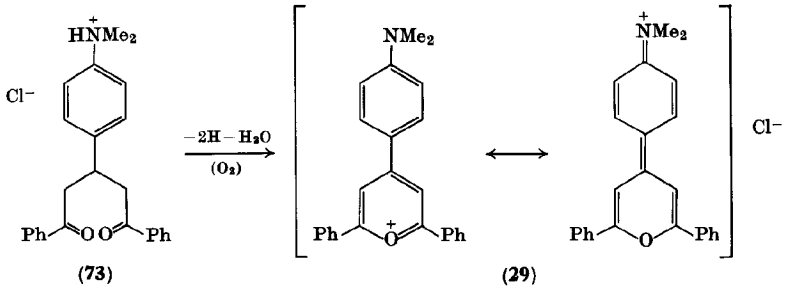


3-Acetyl-6-cyclohexyl-2-methylpyrylium was prepared from 1-cyclohexyl-4-acetyl-1,5-hexanedione, ferric chloride, and conc. hydrochloric acid.[260a]

For obtaining pentaphenylpyrylium from 1,2,3,4,5-pentaphenyl-

[260a] A. G. Ismailov and G. I. Safarov, *Zh. Organ. Khim.* **2**, 1624 (1966).

pentane-1,5-dione only refluxing with phosphorus pentachloride[34,261] or with bromine in acetic acid[262] was effective. Other dehydrogenating agents are perchloric acid or stannic chloride in acetic anhydride,[263–265] bromine or iodine in acetic acid,[262] and antimony pentachloride in acetic anhydride.[166,263] Treibs and Bader[266] found that diketone **73** is converted into the pyrylium salt (**29**)[143] on bubbling air through a suspension of the diketone hydrochloride in ether.



The mechanism of the dehydrogenation was believed by Dilthey to involve ferric chloride as the oxidant and acetic anhydride as the dehydrating agent.[166] Subsequent investigators adopted this view (cf. Lombard and Stephan[267]). One reagent without the other is ineffective.[46] Simalty-Siemiatycki made an important step in elucidating the mechanism when he showed[227] that triphenylmethyl perchlorate in refluxing acetic acid, nitromethane, or acetonitrile is able to perform the conversion **70** → **37** in very good yield. From diphenacylacetic acid, the perchlorate of 2,6-diphenylpyrylium-4-carboxylic acid could be obtained.[227] Unlike acid-dehydrogenating agents, triphenylmethyl perchlorate does not promote intramolecular condensation of the 1,5-dione to a ketol, allowing the preparation of

[261] W. Dilthey and H. Kaffer. *Ber. Deut. Chem. Ges.* **55**, 1275 (1922).
[262] M. Simalty, J. Carretto, and R. Fugnitto, *Bull. Soc. Chim. France* p. 2959 (1966).
[263] C. F. H. Allen and H. R. Sallans, *Can. J. Res.* **9**, 574 (1933).
[264] G. N. Dorofeenko, Z. N. Nazarova, and N. N. Novikov, *Zh. Obshch. Khim.* **34**, 3918 (1964).
[265] G. N. Dorofeenko, G. A. Korolchenko, and S. V. Krivun, *Khim. Geterotsikl. Soedin. Akad. Nauk Latv. SSR* p. 817 (1965).
[266] A. Treibs and H. Bader, *Chem. Ber.* **90**, 789 (1957).
[267] R. Lombard and J. P. Stephan, *Bull. Soc. Chim. France* p. 1458 (1958).

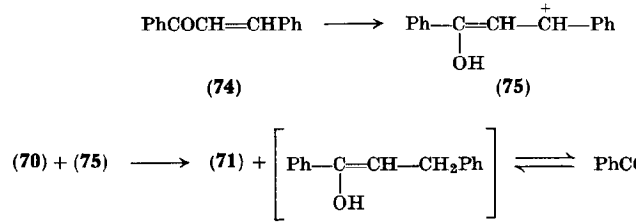
pyrylium salts[268] from the 1,5-diones obtained by condensing aldehydes with two moles of cyclanones,[269-271] and does not affect sensitive substituents like furyl.[265] Balaban[272] showed that similar conversions may be effected with *t*-butyl chloride and aluminum chloride, but *t*-butylation of phenyl substituents occurs as a side process.[273]

2,4,6-Tri-*t*-butylpyrylium can be obtained by dehydrogenating the corresponding 1,5-diketone with triphenylmethyl fluoroborate.[273a] It was shown by Fărcasiu that 1,5-diketones can also be dehydrogenated and dehydrated to pyrylium salts by triphenylmethyl hexachloroantimonate generated *in situ* from chlorotriphenylmethane and antimony pentachloride. Even pentaphenylpyrylium may thus be prepared at room temperature.[273b]

It is known that tropylium may be prepared from tropylidene via hydride abstraction by Ph_3C^+[274] or Me_3C^+[275] carbonium ions; therefore, it is very likely that here too the dehydrogenation is a hydride transfer from the 1,5-dione to an acceptor. A similar dehydrogenation of chromanones to chromones, with triphenylmethyl perchlorate was reported.[276, 276a] A study of the electrooxidation of 1,5-diones on a rotating platinum electrode[277] showed that 1,5-diaryl-substituted diones afford pyrylium salts in these conditions and that the half-wave potentials correlate with yields in chemical dehydrogenations.

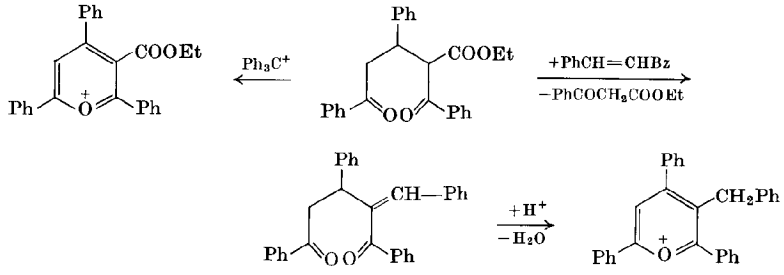
[268] A. T. Balaban and N. S. Bărbulescu, *Rev. Roumaine Chim.* **11**, 109 (1966).
[269] N. S. Bărbulescu, G. Bădită, and M. N. Tilichenko, *Zh. Obshch. Khim.* **33**, 4027 (1963).
[270] M. N. Tilichenko, V. G. Kharchenko, and T. I. Krupina, *Zh. Obshch. Khim.* **34**, 2721 (1964); M. N. Tilichenko, *Zh. Obshch. Khim.* **25**, 2503 (1955); V. A. Khaminski and M. N. Tilichenko, *Khim. Geterotsikl. Soedin. Akad. Nauk Latv. SSR* p. 708 (1967).
[271] G. V. Pavel and M. N. Tilichenko, *Zh. Organ. Khim.* **2**, 2262 (1966).
[272] A. T. Balaban, *Compt. Rend.* **256**, 4239 (1963).
[273] A. T. Balaban, A. R. Katritzky, and B. Semple, *Tetrahedron* **23**, 4001 (1967).
[273a] K. Dimroth and W. Mach, *Angew. Chem.* **80**, 489 (1968); W. Rundel, *Chem. Ber.* **102**, 374 (1969).
[273b] D. Fărcasiu, *Tetrahedron* **25**, (1969) in press.
[274] H. J. Dauben, F. A. Gadecki, K. M. Harmon, and D. R. Pearson, *J. Am. Chem. Soc.* **79**, 4557 (1957).
[275] D. Bryce-Smith and N. A. Perkins, *J. Chem. Soc.* p. 2320 (1961).
[276] A. Schönberg and G. Schütz, *Chem. Ber.* **93**, 1466 (1960).
[276a] B. D. Tilak and Z. Mulijiani, *Tetrahedron* **24**, 949 (1968).
[277] C. Bratu and A. T. Balaban, *Rev. Roumaine Chim.* **10**, 1001 (1965).

As will be discussed in the next section, 1,5-pentanediones are obtained by Michael addition of acetophenones to chalcones. The addition and cyclization may be merged in one step (see Section II, C, 2, g). When acetophenone was condensed with chalcone (**74**) in the presence of $BF_3 \cdot Et_2O$[267, 278] or of $HClO_4$,[272] β-phenylpropiophenone (**76**) was obtained as by-product; its formation is due to hydride transfer to the conjugate acid of chalcone (**75**), which is the acceptor (experimental data and theoretical calculations[279] show that chalcones are protonated at the oxygen atom). Balaban[272] obtained a 72% yield in the conversion **70** → **37** using as acceptor chalcone and as catalysts perchloric or sulfuric acids (i.e., **75**). The formation of β-phenylpropiophenone (**76**) in the Chichibabin synthesis of pyridines from chalcones and ketones in the presence of ammonium acetate,[280] and in the pyrimidine synthesis from chalcones and amidines[281] is undoubtedly due to a similar hydride transfer.



Boron trifluoride etherate,[279a] is also a good catalyst for this hydride transfer to chalcone. Unlike triphenylmethyl perchlorate, however, chalcone is able to enter Michael additions with the 1,5-diketone followed by eliminations leading to unexpected products, e.g., 3-benzyl-2,4,6-triphenylpyrylium from 2-carbethoxy-1,3,5-triphenylpentane-1,5-dione and chalcone; the benzyl group originates from chalcone, the elimination product being ethyl benzoylacetate.[279a]

[278] R. Lombard and J. P. Stephan, *Bull. Soc. Chim. France* p. 1369 (1957).
[279] M. H. Palmer and D. S. Urch, *J. Chem. Soc.* p. 174 (1963); N. C. Deno, H. G. Richey, N. Friedman, J. D. Hodge, J. J. Houser, and C. U. Pitman, *J. Am. Chem. Soc.* **85**, 2991 (1963); D. M. Brouwer, *Tetrahedron Letters* p. 453 (1968).
[279a] J. A. Van Allan and G. A. Reynolds, *J. Org. Chem.* **33**, 1102 (1968).
[280] R. L. Frank and R. P. Seven, *J. Am. Chem. Soc.* **71**, 2629 (1949).
[281] R. M. Dodson and J. K. Seyler, *J. Org. Chem.* **18**, 461 (1951).



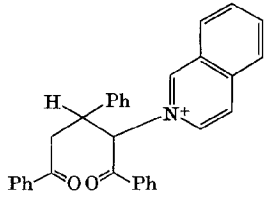
These facts make it very likely that all dehydrogenations of 1,5-pentanediones to pyrylium salts are hydride transfer reactions, and therefore, that Dilthey's idea is incorrect. Indeed, although the contrary was stated,[263] perchloric acid is not an oxidant in these conditions and ferric chloride is probably also not an oxidant. The proposed mechanism[272] for dehydrogenations by Lewis or Brönsted acids and acetic anhydride consists in the formation (evidenced in such systems[282]) of an acetyl carbonium ion, which is the hydride acceptor. The hydride transfer converts it into acetaldehyde[283] (which undergoes further condensations) just as **74** is converted into **76**, Ph_3C^+ into triphenylmethane, and Me_3C^+ into isobutane. Two reported dehydrogenations, by polyphosphoric acid[284] at ca. 50° and by hydrogen bromide in acetic acid, ethanol, or even water,[285] cannot be explained satisfactorily by this mechanism; perhaps part of the 1,5-diketones acts as an acceptor.

Several new methods for the synthesis of 1,5-diones were described recently,[286–288] Although some methods to be discussed further (e.g., type in Section II,C,2,g) obviate the necessity of preparing 1,5-diketones, this synthesis of pyrylium salts by dehydrogenation of 1,5-diones is an important one, and was applied successfully to the preparation of various salts with dissimilar substituents.[220, 289, 290]

[282] H. Burton and P. F. G. Praill, *J. Chem. Soc.* p. 1203 (1950).
[283] C. D. Nenitzescu and C. N. Ionescu, *Ann. Chem.* **491**, 189 (1931).
[284] Z. A. Ariyan and H. Suschitzky, *J. Chem. Soc.* p. 2242 (1961).
[285] W. Dilthey and E. Floret, *Ann. Chem.* **440**, 89 (1924).
[286] G. Stork and R. Borch, *J. Am. Chem. Soc.* **86**, 935 (1964).
[287] Y. Maroni-Barnaud, L. Gorrichon-Guignon, P. Maroni, and J. Bertrand, *Tetrahedron Letters* p. 2243 (1966).
[288] W. Ried and W. Kunstmann, *Chem. Ber.* **100**, 605 (1967).
[289] D. W. Hill, *J. Chem. Soc.* p. 85 (1935).
[290] C. F. H. Allen and W. E. Barker, *J. Am. Chem. Soc.* **54**, 736 (1932).

Recently it allowed the preparation of bispyrylium salts (where the two pyrylium nuclei with aryl groups in positions 2 and 6 are linked in position 4 by *p*-phenylene,[83, 291, 292] *m*-phenylene, or 2,5-thienylene group[83]) by dehydrogenation with perchloric acid in acetic anhydride or with triphenylmethyl perchlorate in acetic acid. Directly linked dications were obtained similarly[292a] (cf. Section II,B,2,a[88a]).

Dilthey[46] wished to adapt, for pyrylium, syntheses which with ammonia were known to yield pyridines. Indeed, there is a marked similarity, and probably a common mechanism between certain syntheses of pyrylium salts and of pyridines, e.g., Chichibabin's and



(77)

Hantzsch's.[2, 3, 205, 293, 294] With the aid of pyrylium salts the structure of Bauer's[295] nonidentified base obtained from **70** (R = R′ = R″ = Ph) and ammonia was assigned as 2,4,6-triphenylpyridine[284] (the same substance that had been described by Delacre[214] as "merodypnopinacoline" and elucidated by Ivanov and Ivanov[215]) and the mechanism of the Reddelien pyridine synthesis was clarified.[296] By continuing this analogy, one could expect that the intermediate **77** in the pyridine synthesis developed by Zecher and Kröhnke[297] ought to yield pyrylium salts on treatment with strong acids, no dehydrogenation being necessary. Though this compound fluoresces in acetic acid like 2,4,6-triphenylpyrylium, it does not form this pyrylium salt with

[291] K. Dimroth, W. Umbach, and K. H. Blöcher, *Angew. Chem.* **75**, 860 (1963).
[292] S. V. Krivun and G. N. Dorofeenko, *Zh. Obshch. Khim.* **34**, 2091 (1964).
[292a] H. Strzelecka and M. Simalty, *Bull. Soc. Chim. France* p. 4122 (1968).
[293] F. Brody and P. R. Ruby, *in* "Pyridine and Its Derivatives" (E. Klingsberg, ed.), Pt. I, p. 210. Wiley (Interscience), New York, 1960.
[294] E. N. Shaw, *in* "Pyridine and Its Derivatives" (E. Klingsberg, ed.), Pt. 2, p. 1. Wiley (Interscience), New York, 1961.
[295] E. Bauer, *Compt. Rend.* **158**, 1680 (1914).
[296] L. Amoros-Marin and R. B. Carlin, *J. Am. Chem. Soc.* **81**, 733 (1959).
[297] W. Zecher and F. Kröhnke, *Chem. Ber.* **94**, 690 (1961).

acids.[238] The formation of pyridines from 1,5-diketones[298, 298a] or 1,5-dialdehydes[299] on treatment with ammonium acetate or hydroxylamine closely parallels the synthesis of pyrylium salts.

C. Two-Component Syntheses

All syntheses to be described in the present Section II,C can be ascribed to the formation of one of the pentane derivatives described in the preceding Section II,B: 2-pentene-1,5-diones, 2,4-pentadien-1-ones, or 1,5-pentanediones. In the first case the reaction does not involve dehydrogenation, in the other two it does. By merging the synthesis of the C_5-chain with the cyclization (and when necessary with the dehydrogenation) into one step, the methods become more convenient and encompass a wider range. In order to lead to cyclized products, the condensations C_4+C_1 or C_3+C_2 must be performed in strongly acid medium; dehydrogenations may be conveniently effected in such media by carbonium ions or other reagents.

1. *From a C_4 and a C_1 Unit*

a. *By Acylation of Unsaturated Ketones.* The reaction leads to 2-pentene-1,5-diones (type in Section II,B,2,a) and does not involve a dehydrogenation step. The first to have investigated the action of anhydrides on a 2-buten-1-one was Gastaldi[47] in 1922, who showed that dypnone (**78**, R=R′=Ph) and acetic anhydride (R″=Me) afforded 2-methyl-4,6-diphenylpyrylium in the presence of anhydrous ferric chloride, i.e., the same salt obtained previously by Dilthey from acetophenone with $Ac_2O+FeCl_3$.[46] Very soon afterward, Schneider and Ross[49] observed independently the same reaction, and thus the structure assignment of diphenylmethylpyrylium salts was corrected (cf. type in Section II,D,2,a). For a discussion concerning priority, see references 48 and 68.

Subsequently both Gastaldi and Peyretti[300] and Schneider[68] performed the reaction with other anhydrides (R″=Et, Pr, iso-Bu). The series was extended by Hopf and Le Fèvre[301] and by others[296]

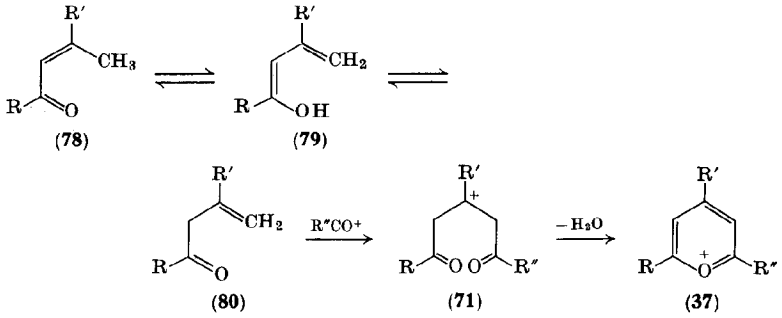
[298] J. E. Downes, *J. Chem. Soc.* **C**, 1491 (1967).
[298a] G. Vanags, E. I. Stankevich and E. Ya. Gren, *Zh. Obshch. Khim.* **30**, 1620 (1960).
[299] Y. I. Chumakov and L. P. Lugowskaya, *Zh. Obshch. Khim.* **34**, 3515 (1964).
[300] C. Gastaldi and G. L. Peyretti, *Gazz. Chim. Ital.* **53**, 11 (1963).
[301] P. P. Hopf and R. J. W. Le Fèvre, *J. Chem. Soc.* p. 1989 (1938).

who employed various aliphatic or aromatic anhydrides or acid chlorides as acylating agents and ferric chloride as catalyst. The yields are higher with chlorides than with anhydrides and with aliphatic than with aromatic acids. The reaction was also applied to aliphatic unsaturated ketones, namely, to mesityl oxide (**78**, R=R′=Me) and acetic anhydride (R″=Me) by Schneider and Sack,[302] who employed sulfoacetic acid as catalyst (also cf. Gottesmann[303] for this catalyst), and by Diels and Alder who used perchloric acid.[304] A more classic Friedel–Crafts acetylation of mesityl oxide with acid chlorides (R″=Me, Et, Ph) and aluminum chloride or stannic chloride was carried out by Balaban and Nenitzescu.[305] Elderfield and King[306] described the formation of 2,4,6-triphenylpyrylium fluoroborate from dypnone and benzoyl fluoride in the presence of boron trifluoride etherate. The observations made by Baddeley and Khayat, and by Fărcasiu and Balaban, on the acetylation of unsaturated β-chloro, and β-hydroxy ketones will be discussed in Section II,D,3,a.

An interesting application of this reaction was the use of macromolecular anhydrides, namely, styrene–maleic anhydride or vinyl acetate–maleic anhydride copolymers; in the presence of perchloric acid as catalyst, these copolymers acylate mesityl oxide or dypnone to macromolecular pyrylium salts which, with aryl substituents, are fluorescent.[307, 308] No crystalline products could be obtained from succinic anhydride because of the solubility and ease of decarboxylation.

The limitations of the reaction consist in the nonavailability of suitably substituted 2-buten-1-ones (**78**), in the moderate yields (usually up to 40%) and poor purity of the products, and in the fact that in most cases at least three substituents are required in positions 2, 4, and 6 of the resulting pyrylium salt for its isolation. Ethylideneacetone (**78**, R=Me, R′=H) and crotonaldehyde (**78**, R=H, R′=Me) failed to yield pyrylium salts on acetylation with $AcCl+AlCl_3$;[305] however, acetylation with $Ac_2O+HClO_4$ of β-hydroxyaldehyde

[302] W. Schneider and A. Sack, *Ber. Deut. Chem. Ges.* **56**, 1786 (1923).
[303] E. Gottesmann, *Ber. Deut. Chem. Ges.* **66**, 1168 (1933).
[304] O. Diels and K. Alder, *Ber. Deut. Chem. Ges.* **60**, 716 (1927).
[305] A. T. Balaban and C. D. Nenitzescu, *Ann. Chem.* **625**, 74 (1959).
[306] R. C. Elderfield and T. P. King, *J. Am. Chem. Soc.* **76**, 5437, 5439 (1954).
[307] J. Petit and L. Strzelecki, *Compt. Rend.* **257**, 2654 (1963).
[308] L. Strzelecki, *Bull. Soc. Chim. France* p. 2666 (1967); *Compt. Rend.* **C265**, 1097 (1967).



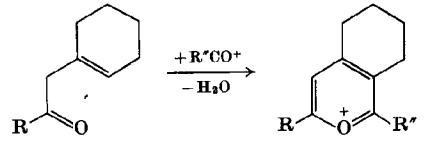
(78) (79) (80) (71) (37)

acetals afforded pyrylium salts unsubstituted in an α-position (2,4-dimethylpyrylium could not be isolated, but treatment of the reaction mixture with ammonia afforded 2,4-lutidine).[309] In special cases, e.g., for 2,4,6-trimethylpyrylium perchlorate from mesityl oxide, acetic anhydride, and perchloric acid,[304, 310] the method gives satisfactory results. It is best indicated, however, for preparing pyrylium salts where the R, R′, and R″ groups are all different; the ketone (**78**) is first prepared by aldol condensation, then acylated.

The reaction mechanism has been discussed by several earlier authors;[59, 311] more recently, Elderfield and King[306] proposed that the enol form (**79**) of the ketone underwent acylation, whereas Balaban and Nenitzescu[305] assumed that the β,γ-unsaturated isomer (**80**) of the ketone was acylated. Support for the latter view is given by the high concentration of the β,γ-unsaturated isomer (**80**) in equilibrium with the α,β-isomer (**78**).[312–321] In the case of mesityl

309 G. I. Zhungietu and E. M. Perepelitsa, *Zh. Obshch. Khim.* **36**, 1858 (1966).
310 K. Hafner, *Org. Synth.* **44**, 96 (1964).
311 W. Schneider and H. Keller, *Ber. Deut. Chem. Ges.* **74**, 729 (1941).
312 C. Harries, *Ber. Deut. Chem. Ges.* **32**, 1326 (1899); *Ann. Chem.* **330**, 185 (1904).
313 H. Hibbert, *J. Am. Chem. Soc.* **37**, 1748 (1915).
314 J. Doeuvre, *Bull. Soc. Chim. France Ser. 4* **39**, 1594 (1926).
315 H. C. Volger and W. Brockman, *Rec. Trav. Chim.* **84**, 1017 (1965).
316 G. Hesse, R. Hatz, and U. Dutt, *Chem. Ber.* **100**, 923 (1967).
317 G. Dupont and L. Menut, *Bull. Soc. Chim. France Ser. 5* **6**, 1215 (1939).
318 J. Kenyon and D. P. Young, *J. Chem. Soc.* p. 1547 (1940).
319 F. H. Stross, J. M. Monger, and H. de V. Finch, *J. Am. Chem. Soc.* **69**, 1627 (1947).
320 H. F. Gray, R. S. Rasmussen, and D. D. Tunnicliff, *J. Am. Chem. Soc.* **69**, 1630 (1947).
321 J. Wiemann and L. Martineau, *Compt. Rend.* **246**, 131 (1958).

oxide, the equilibrium concentration is ca. 9%.[315, 316] The isomers can be separated[319] by careful fractionations avoiding acidic or alkaline catalysts which immediately restore the equilibrium. Praill and Whitear[322] showed that by acetylating ($Ac_2O + HClO_4$) 4-methyl-4-penten-2-one (isomesityl oxide) (**80**) instead of mesityl oxide (**78**), the yield of trimethylpyrylium perchlorate was raised from ca. 40 to 87%, which strongly suggests that **80** is the active form (the $C{=}CH_2$ group, not being conjugated with the carbonyl group, behaves normally). A case in which a β,γ-unsaturated isomer prevails owing to conformational reasons is that of cyclohexenylacetone (**81**, R = Me) or cyclohexenylacetophenone (**81**, R = Ph) which lead to Bz-tetrahydroisochromylium salts (**82**) in 50–90% yields, as shown by Dorofeenko and co-workers.[323–327] By the irreversible formation of the resonance-stabilized pyrylium cation, the equilibrium (**78** $\rightleftharpoons$ **80**) is shifted to the right. This method allowed the prepration of 5,6,7,8-tetrahydroisobenzopyrylium salts (**82**) with *p*-anisyl substituents[328]; by starting from 5- or 7-membered cycloalkanones, pyrylium salts with fused saturated rings were prepared.[329, 330] Pulegone also



(81) (82)

322 P. F. G. Praill and A. L. Whitear, *J. Chem. Soc.* p. 3573 (1961).
323 G. N. Dorofeenko and V. I. Dulenko, *Zh. Obshch. Khim.* **32**, 3445 (1962).
324 L. V. Dulenko, V. I. Dulenko, and G. N. Dorofeenko, *Zh. Obshch. Khim.* **34**, 3588 (1964).
325 G. N. Dorofeenko, V. I. Dulenko, and L. V. Dulenko, *Zh. Obshch. Khim.* **34**, 3116 (1964).
326 G. N. Dorofeenko and V. I. Dulenko, *Dokl. Akad. Nauk SSSR* **157**, 361 (1964).
327 G. N. Dorofeenko, G. P. Safaryan, and V. I. Dulenko, *Zh. Obshch. Khim.* **36**, 811 (1966).
328 G. N. Dorofeenko, Habilitation Thesis, Rostov/Don, 1965; S. V. Krivun, Ph.D. Thesis, Rostov/Don, 1965; V. I. Dulenko, Ph.D. Thesis, Rostov/Don, 1965.
329 G. N. Dorofeenko, Y. A. Zhdanov, V. I. Dulenko, V. A. Palchkov, and N. V. Kovalenko, *Khim. Geterotsikl. Soedin. Akad. Nauk Latv. SSR* p. 172 (1966).
330 Y. A. Zhdanov, G. N. Dorofeenko, and V. A. Palchkov, *Khim. Geterosikl. Soedin. Akad. Nauk Latv. SSR* p. 812 (1965).

affords on acetylation a pyrylium salt.[331] *N*-Alkyl-indolyl-acetones and similar glycosidic derivatives are acylated to indole[2,3-^{c}]-pyrylium salts.[331a,b]

Acylation of indenylindenones leads to indenopyrylium salts.[332] A related reaction is the acylation of 3,4-disubstituted benzyl ketones to isobenzopyrylium salts[333–337]; the unsubstituted compounds yield 4-pyrones as shown in Section II,D,3,a. Another related acylation converts unsaturated esters into 2-pyrones, e.g., ethyl β,β-dimethyl-acrylate into 4,6-dimethyl-2-pyrone.[109]

The anhydride or acyl chloride and the catalyst (proton acid or Lewis acid) interact leading to the acylating agent [formulated here for brevity as an acyl cation (**83**)].[13, 14, 282, 338, 339]

$$(R{-}CO)_2O + HX \longrightarrow R{-}CO^+X^- + RCOOH$$
$$(R{-}CO)_2O + MHal_n \longrightarrow R{-}CO^+ + RCOOMHal_n^-$$
$$R{-}COHal + MHal_n \longrightarrow R{-}CO^+ + MHal_{n+1}^-$$
$$R{-}COOH + 2HX \longrightarrow R{-}CO^+X^- + H_3O^+X^-$$
(**83**)

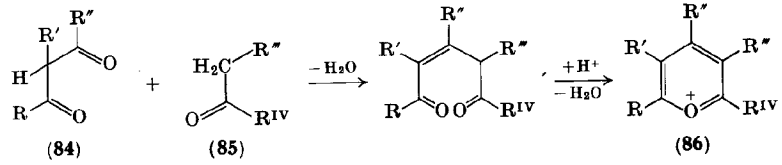
b. *From Unsaturated Ketones and Aldehydes, with Dehydrogenation.* This reaction leads to 2,4-pentadien-1-ones (type in Section II,B,2,e)

[331] G. N. Dorofeenko and G. I. Zhungietu, *Zh. Obshch. Khim.* **35**, 963 (1965).
[331a] G. N. Dorofeenko and V. I. Dulenko, USSR Patent No. 194,093 (1967).
[331b] Yu. A. Zhdanov, V. I. Kornilov, and G. N. Dorofeenko, *Dokl. Akad. Nauk SSSR* **178**, 849 (1968); G. N. Dorofeenko and V. G. Korobkova, *Chem. Ind.* (*London*) p. 1848 (1968).
[332] Y. A. Zhdanov, G. N. Dorofeenko, and V. A. Palchkov, *Zh. Obshch. Khim.* **35**, 827 (1965).
[333] G. N. Dorofeenko, S. V Krivun, and V. I. Dulenko, USSR Patent No. 176,592 (1965).
[334] G. N. Dorofeenko, L. V. Dulenko, V. I. Dulenko, and S. V. Krivun, *Zh. Organ. Khim.* **1**, 1171 (1965).
[335] G. N. Dorofeenko, A. D. Semenov, V. I. Dulenko, and S. V. Krivun, *Zh. Organ. Khim.* **2**, 1492 (1966).
[336] G. N. Dorofeenko, E. V. Kuznetsov, and S. V. Krivun, *Zh. Organ. Khim.* **2**, 1499 (1966).
[337] S. V. Krivun, V. I. Dulenko, L. V. Dulenko, and G. N. Dorofeenko, *Dokl. Akad. Nauk SSSR* **166**, 359 (1966); G. N. Dorofeenko, E. I. Sadekova, S. V. Krivun, and Y. A. Zhdanov, *Dokl. Akad. Nauk SSSR* **181**, 345 (1968).
[338] H. Burton and P. F. G. Praill, *Quart. Rev.* (*London*) **6**, 302 (1952).
[339] D. P. N. Satchell, *Quart. Rev.* (*London*) **17**, 160 (1963); D. P. N. Satchell, *in* "The Chemistry of the Carbonyl Group" (S. Patai, ed.), p. 233. Wiley (Interscience), New York (1966); G. A. Olah and A. M. White, *J. Am. Chem. Soc.* **89**, 7072 (1967).

by crotonic condensation. Hopf and Le Fèvre observed[301] that dypnone condenses with acetaldehyde or benzaldehyde in the presence of ferric chloride, yielding the same pyrylium salts (2-methyl-4,6-diphenylpyrylium and 2,4,6-triphenylpyrylium, respectively) as when acid (acetyl or benzoyl) derivatives are employed (type in Section II,C,1,a). The above authors supposed that it is not the aldehyde which undergoes oxidation, but the crotonic condensation product (**63**, R = R′ = Ph, R″ = Me or Ph), i.e., a reaction of the type in Section II,B,2,e.

2. *From a C_3- and a C_2-Unit*

a. *From 1,3-Diketones and Methyl(ene) Ketones.* By crotonic condensation of enolizable β-diketones (**84**) with methyl or methylene ketones (**85**), a 2-pentene-1,5-dione is formed, which does not require dehydrogenation to form a pyrylium salt (type in Section II,B,2,a).

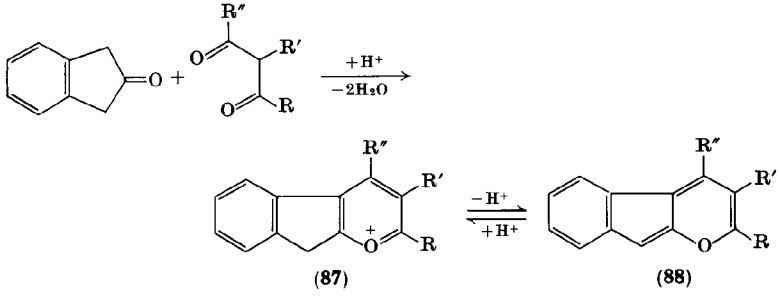


This type of reaction was first used by Dilthey and Fischer[69] in connection with the mechanism of the type in Section II,D,2. By analogy with the well-known formation of benzopyrylium salts from methyl(ene) ketones and *o*-hydroxybenzaldehyde or *o*-hydroxy-acetophenone,[340] benzoylacetone (**84**, R = Me, R′ = H, R″ = Ph) and acetophenone (**85**, R^{IV} = Ph, R‴ = H) afforded in the presence of acetic anhydride and sulfuric acid, 2-methyl-4,6-diphenylpyrylium sulfoacetate. The interesting feature of this reaction is that a unique product is obtained (i.e., only the carbonyl group of the diketone adjacent to the phenyl enters the condensation, although two such groups are available); R and R″ could be reversed, but they are not.[59, 69] Similarly, dibenzoylmethane (**84**, R = R″ = Ph, R′ = H) afforded 2,4,6-triphenylpyrylium with acetophenone in 80% yield.[69]

Revived interest in this type of reaction is now apparent. Schroth

[340] S. Wawzonek, *in* "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 2. Wiley, New York, 1951.

and Fischer[341,342] and Dorofeenko with his co-workers[343] demonstrated the potentialities of the method for varying the substituents of pyrylium salts (**86**). It was believed initially that at least three substituents in positions 2, 4, and 6 were required. However, β-keto aldehydes (hydroxymethylene ketones) react smoothly with ketones and perchloric acid in acetic acid affording 4-unsubstituted pyrylium salts.[344,345] This method allowed the preparation of pyrylium salts with fused saturated rings[82,346,347] (cf. Section II,B,2,f) or fused steroid systems.[348–350] With few exceptions the ketone **85** must have at least one aromatic or heterocyclic substituent R‴ or R^{IV}. The condensation of 2-indanones with β-diketones takes place in the presence of perchloric acid even at −10° and affords indeno[2,3-*b*]-pyrylium salts (**87**)[341] (cf. **46**) which are deprotonated reversibly to



(87) (88)

341 W. Schroth and G. Fischer, *Z. Chem.* **3**, 147 (1963).
342 W. Schroth and G. Fischer, *Z. Chem.* **3**, 277 (1963).
343 S. V. Krivun, J. V. Shian, and G. N. Dorofeenko, *Zh. Obshch. Khim.* **34**, 167 (1964).
344 G. N. Dorofeenko and G. I. Zhungietu, USSR Patent No. 181,096 (1966); *Chem. Abstr.* **65**, 10567 (1966).
345 G. N. Dorofeenko and G. I. Zhungietu, *Zh. Obshch. Khim.* **35**, 589 (1965).
346 G. N. Dorofeenko, Y. A. Zhdanov, G. I. Zhungietu, and S. V. Krivun, *Tetrahedron* **22**, 1821 (1966); **23**, 1565 (1967).
347 G. N. Dorofeenko, G. V. Lazurievski, and G. I. Zhungietu, *Dokl. Akad. Nauk SSSR* **161**, 355 (1965).
348 G. I. Zhungietu and G. N. Dorofeenko, *Usp. Khim.* **36**, 48 (1967).
349 G. I. Zhungietu, G. N. Dorofeenko, and G. V. Lazurievski, *Dokl. Akad. Nauk SSSR* **163**, 372 (1965).
350 G. I. Zhungietu, L. N. Volovelski, G. N. Dorofeenko, and G. V. Lazurievski, *Khim. Prirodn. Soedin., Akad. Nauk USSR* p. 318 (1965); G. N. Dorofeenko, L. N. Volovelski, and B. M. Savin, *Zh. Obshchei Khim.* **38**, 2686 (1968).

colored anhydro bases of benzoxalene class (**88**)[351] (cf. **44**). The diketone can have aliphatic, aromatic, or heterocyclic R, R′, R″ substituents.

Krivun, Shian, and Dorofeenko[343] condensed acetylacetone or dibenzoylmethane with various ketones (acetone, acetophenone, acetothienone, 1-acetylnaphthalene, or 5-acetylacetaphthene) and obtained pyrylium salts in 10–20% yield in the presence of perchloric acid.

An extension of this synthesis would be the condensation of β-keto esters with ketones leading to alkoxypyrylium salts and hence to 2- or 4-pyrones; however, attempts at such reactions were unsuccessful.[352]

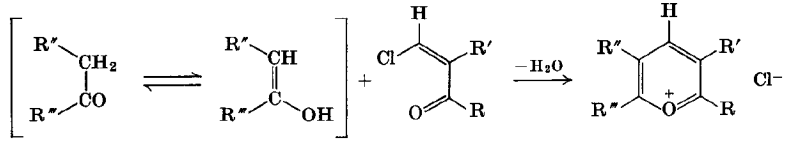
The formation of pyrylium salts from methyl(ene) ketones and 1,3-diketones, e.g., of 2,4,6-triphenylpyrylium from acetophenone and dibenzoylmethane, has an interesting counterpart in several reactions of pyrylium salts. With nucleophiles like phenylhydrazine,[353] hydroxylamine,[353] or benzylmagnesium chloride,[178–180] 2,4,6-triphenylpyrylium forms unstable 2,4-dien-1-ones or 4*H*-pyrans, which rearrange easily to more stable pyrazolines, isoxazolines, or 2*H*-pyrans; on treatment with strong acids, both types of product split off acetophenone, yielding 1,3,5-triphenylpyrazole, 3,5-diphenylisoxazole, and 1,3-diphenylnaphthalene, respectively. These same products can be obtained directly from the above nucleophiles and dibenzoylmethane.[66,354–357] The condensation of methyl(ene) ketones with 1,3-diketones yielding pyrylium salts can, therefore, be considered reversible in a certain sense.

b. *From β-Chlorovinyl Ketones and Methyl(ene) Ketones.* β-Chlorovinyl ketones (**89**)[358–360] have a reactive chlorine atom because they are vinylogs of acid chlorides, e.g., they give Friedel–Crafts reactions

351 G. Fischer and W. Schroth, *Z. Chem.* **3**, 191 (1963).
352 G. Fischer, Ph.D. Thesis, Univ. of Leipzig, 1965.
353 A. T. Balaban, *Tetrahedron* **24**, 5059 (1968); cf. also P. L. Kumler, C. Pedersen and O. Buchardt, *Acta Chem. Scand.* **22**, 2719 (1968).
354 A. T. Balaban and A. Barabas, *Chem. Ind. (London)* p. 404 (1967).
355 P. Canonne and L. C. Leitch, *Can. J. Chem.* **45**, 1761 (1967).
356 P. Canonne, P. Holm, and L. C. Leitch, *Can. J. Chem.* **45**, 2151 (1967).
357 P. Canonne and L. C. Leitch, *Tetrahedron Letters* p. 1757 (1967).
358 M. Julia, *Ann. Chim. (Paris)* **5**, 595 (1950).
359 N. K. Kochetkov, *Usp. Khim.* **24**, 32 (1955).
360 A. E. Pohland and W. R. Benson, *Chem. Rev.* **66**, 161 (1966).

with aromatic hydrocarbons in the presence of tin tetrachloride leading to chalcones.[361] With phenols and naphthols they afford benzo- and naphthopyrylium salts,[362,363] at the same time they are potential β-diketones (cf. their hydrolysis). Thus, their reaction with ketones can be considered as a modified type of synthesis from Section II,C,2,a; on the other hand, while the type in Section II,C,1, was the reaction of an acid chloride with a vinylogous methyl ketone, the present type in this section can be considered as the reaction of a vinylogous acid chloride (**89**) with a methyl ketone (**85**).

A particular advantage of this method is that it can yield only pyrylium salts with the 4-position unsubstituted.



(85) (89) (90)

As shown by Fischer and Schroth,[364] β-chlorovinyl ketones (**89**) react with ketones (**85**) in the presence of $HClO_4$, $FeCl_3$, or other Friedel–Crafts catalysts like $SnCl_4$ in CCl_4, yielding pyrylium salts (**90**). For instance, 2-tetralone (**91**) affords with aromatic or aliphatic β-chlorovinyl ketones 5,6-dihydronaphtho[2.1-*b*]pyrylium salts (**92**); acetophenone and phenyl β-chlorovinyl ketone give 2,6-diphenylpyrylium; with the cyclic β-chlorovinyl ketone (**93**), 2-tetralone yields the pentacyclic system (**94**). Cycloalkanones and β-chlorovinyl ketones lead to pyrylium salts with fused saturated rings. The ketovinylation of 1,3-diketones followed by ketonic splitting[364a,b] should also afford pyrylium salts.

[361] V. F. Belyaev, N. M. Iatsevich, and N. A. Sokolov, *Zh. Obshch. Khim.* **32**, 2022 (1962).

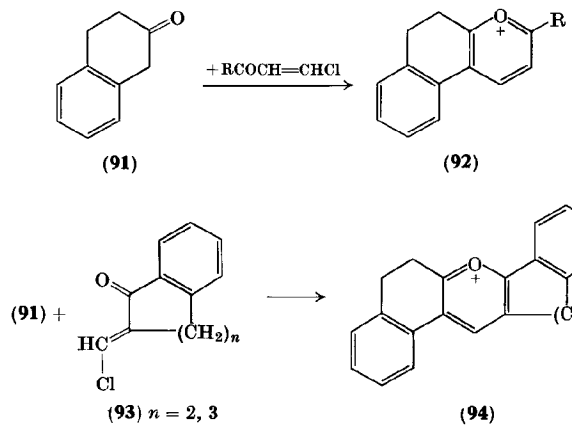
[362] A. N. Nesmeyanov, N. K. Kochetkov, and M. I. Rybinskaya, *Dokl. Akad. Nauk SSSR* **93**, 71 (1953).

[363] N. K. Kochetkov, E. E. Nifantiev, and N. V. Molodstov, *Zh. Obshch. Khim.* **29**, 2330 (1959).

[364] G. Fischer and W. Schroth, *Z. Chem.* **3**, 266 (1963).

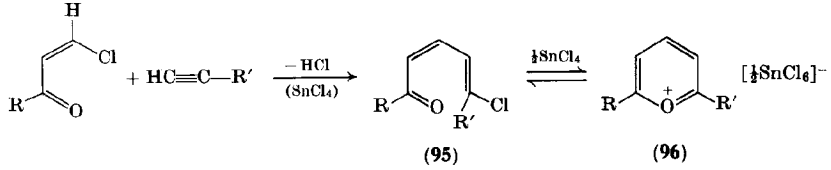
[364a] N. K. Kochetkov and B. P. Gottich, *Zh. Obshch. Khim.* **30**, 948 (1960).

[364b] N. K. Kochetkov, L. J. Kudryashov and B. P. Gottich, *Tetrahedron*, **12**, 63 (1961).



(91) (92) (91) + (93) *n* = 2, 3 (94)

c. *From β-Chlorovinyl Ketones and Acetylenes.* As emphasized in several other instances, e.g., in Sections II,B,2,c; C,2,d; C,2,h; D,1,c, an acetylene may successfully replace a methyl(ene) ketone in pyrylium syntheses. Therefore, one could expect that acetylenes should afford pyrylium salts by reaction with 1,3-diketones or β-chlorovinyl ketones. Whereas until now no example for the former possibility was reported, Schroth and Fischer,[19,364c] and Schmidt[365] found that phenylacetylene reacts smoothly and exothermally with phenyl β-chlorovinyl ketone in chloroform with stannic chloride as catalyst and anion-forming reagent, affording 2,6-diphenylpyrylium hexachlorostannate (cf. Section II,B,2,e).



(95) (96)

Compound **95**, a 5-chloro-2,4-pentadien-1-one; is a doubly vinylogous acid chloride. The addition of β-chlorovinyl ketones to acetylenes was known to afford such compounds as **95**,[366,367] but the valence

[364c] See footnote on p. 190 of Ref. 19.

[365] R. R. Schmidt, *Chem. Ber.* **98**, 334 (1965).

[366] G. Martin, *Ann. Chim. (Paris)* Ser. 13. **4**, 541 (1959).

[367] N. K. Kochetkov and V. Belyaev, *Zh. Obshch. Khim.* **30**, 1495 (1960).

isomerization to pyrylium salts (**96**) requires a Friedel–Crafts catalyst (cf. also the conversion **65** → **66**[257]).

Since β-chlorovinyl ketones are reaction products of acetylenes with acid chlorides, the isolation of these lachrymatory and unstable intermediates is not necessary, as shown by Section II,D,2,d.

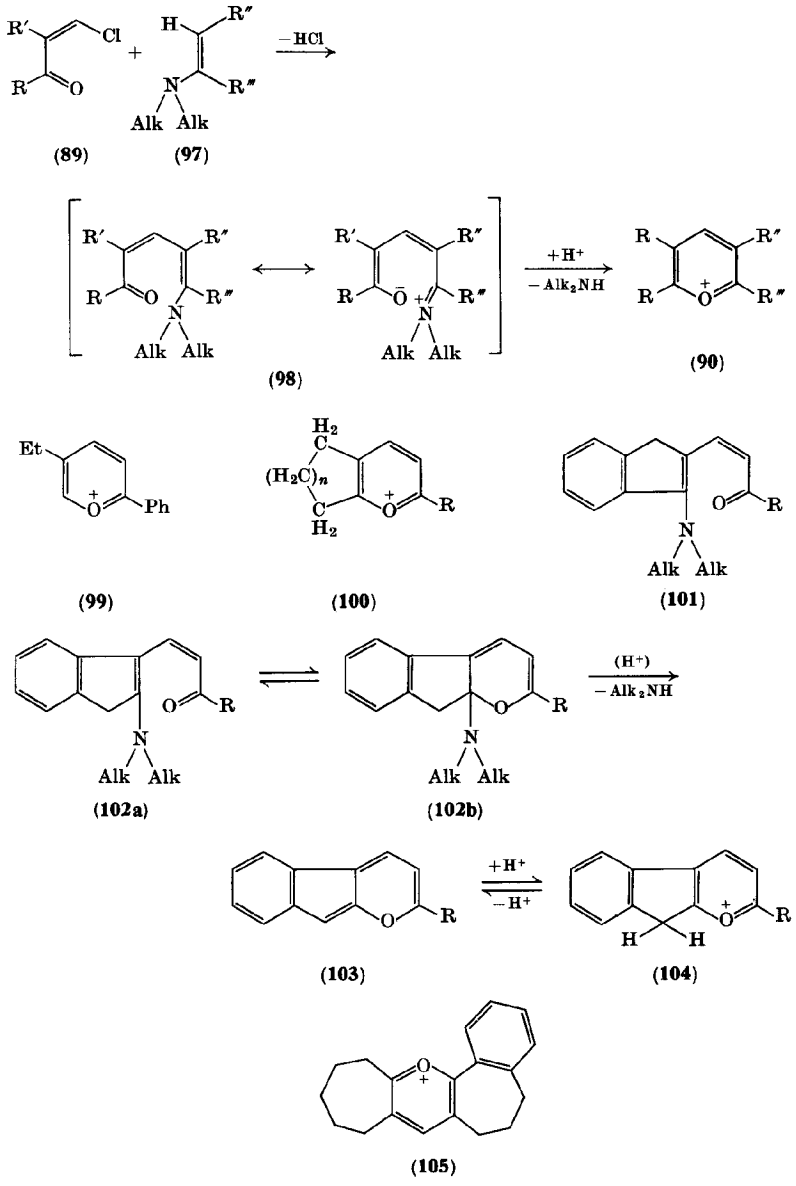
d. *By Dehydrogenative Condensation of β-Chloro Ketones with Acetylenes.* As an extension of the preceding synthesis (Section II,C,2,c), Schmidt showed[365] that 3-chloro-1,3-diphenylpropan-1-one condenses with phenylacetylene in the presence of $SnCl_4$, yielding 2,4,6-triphenylpyrylium. The catalyst acts at the same time as a condensing and dehydrogenating (hydride transfer) agent.

Presumably, β-chloro ketones could also react similarly with methyl(ene) ketones. Another logical extension is the possibility of synthesizing pyrylium salts by dehydrogenative condensation of β-chlorovinyl ketones with olefins like styrene, in the presence of stannic chloride (the olefins so far tested, like isobutene,[359, 360, 366, 367] are not suitable structurally).

e. *From β-Chlorovinyl Ketones and Enamines.* Being potential ketones,[342] enamines are able to replace the ketonic component **85** in the preceding syntheses in Sections II,C,2,a and C,2,b. Schroth and Fischer[368] found that in the absence of catalysts, enamines (**97**) react with β-chlorovinyl ketones (**89**) giving colored compounds (**98**) which correspond to the adducts obtained from pyrylium salts and secondary amines by Lombard and Kress.[369] These adducts form pyrylium perchlorates (**90**) on treatment with perchloric acid. Starting from enamines derived from aldehydes, 2,5-disubstituted pyrylium salts with unsubstituted 4- and 6-positions could be prepared for the first time, e.g., 1-(*N*,*N*-diethylamine)-1-butene and phenyl-β-chlorovinyl ketone react to give 2-phenyl-5-ethylpyrylium perchlorate (**99**). Enamines derived from cyclic ketones, e.g., 1-piperidinocyclopentene, 1-piperidinocyclohexene, or 1-piperidinocycloheptene, afford bicyclic pyrylium salts (**100**, R = Alk or Ar, $n = 1$, 2, or 3). Although the compound **101** obtained from 1-pyrrolidinoindene cannot be converted into a pyrylium perchlorate, the corresponding compounds obtained from 2-piperidinoindene (**102 a**, **b**, R = Alk or Ar) split off readily a secondary amine (i.e., piperidine) forming colored benzoxalene

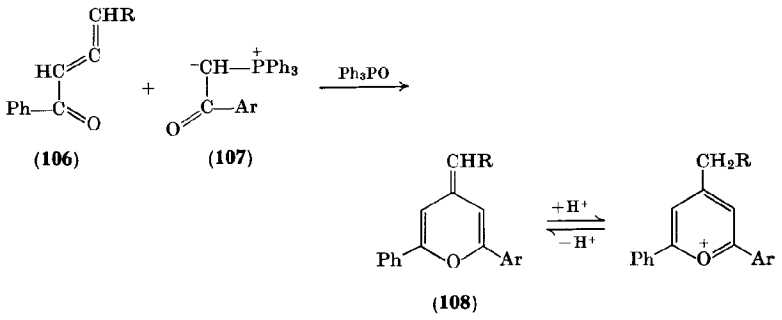
[368] W. Schroth and G. Fischer, *Angew. Chem.* **75**, 574 (1963); *Angew. Chem. Intern. Ed. English* **2**, 394 (1963).

[369] R. Lombard and A. Kress, *Bull. Soc. Chim. France* p. 1528 (1960).



anhydro bases (**103**); these can be reversibly protonated to indeno-[2.1-*b*]pyrylium salts (**104**). Similarly, cyclic β-chlorovinyl ketones can react with enamines, e.g., **93** ($n=3$) yields the pyrylium salt **105** by reacting with piperidinocycloheptene.

f. *From Allenic Ketones and Acylmethylenetriphenylphosphoranes.* In connection with the type in Section II, D, 1, a, Strzelecka, Simalty-Siemiatycki and Prévost[88, 248] obtained the acylmethylenepyran **108** from 1,3-dibenzoylallene (**106**, R = COPh) and the acylmethylene-triphenylphosphorane **107**. The mechanism will be discussed together with that of type in Section II, D, 1, a.

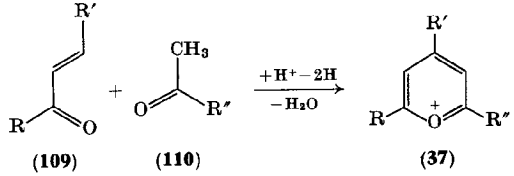


(**106**) (**107**) (**108**)

g. *By Dehydrogenating Condensation of Unsaturated Ketones with Methyl(ene) Ketones.* Michael addition of aryl methyl ketones (**110**), such as acetophenone, to chalcones (**109**) affords 1,5-pentanediones. The reaction is usually carried out in alkaline medium, but it can also be accomplished under the action of strongly acidic catalysts. If a hydride acceptor is also present, the reaction product is a pyrylium salt. Dilthey discovered that chalcone and acetophenone afford with acetic anhydride and ferric chloride 2,4,6-triphenylpyrylium,[46] and afterward made extensive use of this method which allows the unequivocal synthesis of various 2,4,6-trisubstituted pyrylium salts (**37**). With aromatic groups R, R′, and R″, the synthesis is generally successful. Thus, Dilthey obtained 2-aryl-4,6-diphenylpyrylium either from chalcone (**109**, R = R′ = Ph) and *p*-substituted acetophenones (**110**, R″ = aryl) or from (**109**, R = aryl, R′ = Ph) and acetophenone (**110**, R″ = Ph), where the aryl was *p*-anisyl,[370] *p*-tolyl,[166] or *p*-bromophenyl.[166] In all cases the products obtained by alternative paths were identical. *p*-Anisylidene-acetophenone (**109**, R = Ph, R′ = *p*-anisyl)

[370] W. Dilthey, *Ber. Deut. Chem. Ges.* **52**, 1195 (1919).

affords with acetophenone (**110**, R″ = Ph) 2,6-diphenyl-4-*p*-anisyl-pyrylium[371] and with *p*-methoxyacetophenone (**110**, R″ = *p*-anisyl), 2,4-di-*p*-anisyl-6-phenylpyrylium.[20] This reaction was applied to the preparation of various *p*-methoxy- and *p*-hydroxyphenyl-substituted pyrylium salts,[372] of 2-(*m*-anisyl)-4,6-diphenylpyrylium,[373] and of *p*-biphenylyl, *p*-tolyl-, *p*-chlorophenyl-, or 1- and 2-naphthyl-pyrylium salts.[166] In the preparation of 2,6-di-(*p*-hydroxyphenyl)-4-phenylpyrylium[370] (**37**, R = R″ = *p*-HOC_6H_4, R′ = Ph) or 4-(*p*-acetylaminophenyl)-2,6-diphenylpyrylium,[374] zinc chloride may be used instead of ferric chloride; similarly, sulfuric acid may replace ferric chloride in the preparation of amino-, methoxy-, or hydroxy-phenylpyrylium salts.[375] Better yields are obtained in the presence of boron fluoride.[376] The efficiency of nonoxidizing catalysts like $ZnCl_2$ or BF_3 makes it probable that the dehydrogenation is a hydride transfer to an acetyl cation formed from acetic anhydride and the Friedel–Crafts catalyst; in the absence of Ac_2O, acetophenone reacts with chalcone and perchloric acid yielding triphenylpyrylium (**3**) and reducing part of the chalcone[272] as discussed in Section II, B, 2, f. A different method consists in using as condensating and dehydrogenating agent hot sulfuric acid or phosphorus oxychloride; a small amount of selenium as oxidant markedly increases the yield.[377]



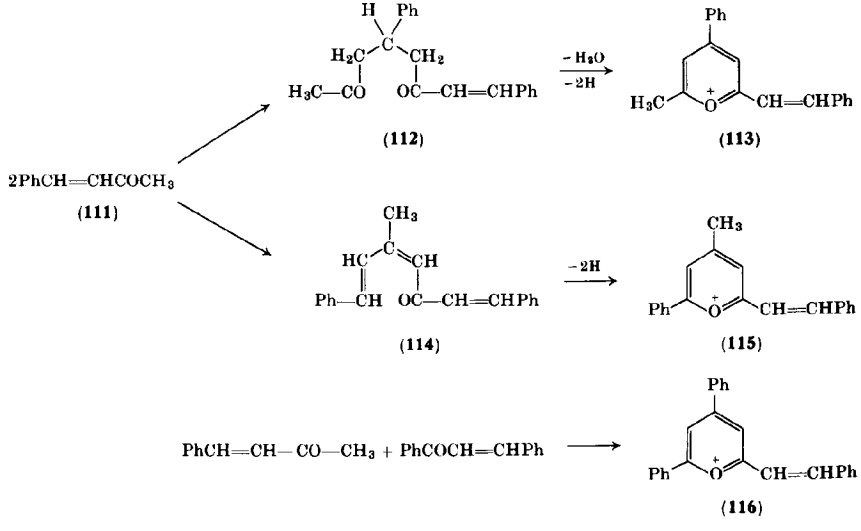
(**109**) (**110**) (**37**)

Ethyl acetoacetate reacts with chalcone in the presence of boron fluoride etherate affording 3-carbethoxy-2-methyl-4,6-diphenylpyrylium; this can be hydrolyzed and decarboxylated to 2-methyl-4,6-diphenylpyrylium[279a] which should theoretically result from acetone and chalcone.

[371] W. Dilthey and R. Taucher, *Chem. Ber.* **53**, 252 (1960).
[372] W. Dilthey, G. Frode, and H. Koenen, *J. Prakt. Chem.* **114**, 153 (1926).
[373] W. Dilthey and C. Bloss, *J. Prakt. Chem.* **101**, 207 (1921).
[374] W. Dilthey and C. Berres, *J. Prakt. Chem.* **111**, 340 (1925).
[375] W. Dilthey and W. Radmacher, *J. Prakt. Chem.* **111**, 153 (1925).
[376] W. C. Dovey and R. Robinson, *J. Chem. Soc.* p. 1389 (1935).
[377] R. Wizinger, S. Losinger, and P. Ulrich, *Helv. Chim. Acta* **39**, 5 (1956).

Although this method was used by Dilthey for preparing a large number of 2,4,6-triarylpyrylium salts, especially with hydroxy, methoxy, and amino groups,[372, 374, 375] he found a few limitations. Methylene ketones, e.g., deoxybenzoin, do not react like methyl ketones (**110**); 2,4,6-tri-*p*-anisylpyrylium cannot be prepared by this method with $FeCl_3$ but only by alkaline Michael condensation to the respective 1,5-pentanedione followed by dehydrogenation,[34] or by replacing $FeCl_3$ by BF_3.[376] The formation of 2,6-diphenyl-4-*p*-dimethylaminophenylpyrylium from acetophenone and *p*-dimethylaminobenzylidene-acetophenone, which does not succeed in the presence of ferric chloride and acetic anhydride, proceeds satisfactorily with hot sulfuric acid.[143]

More serious limitations and precautions apply to compounds in which not all three R, R′, and R″ groups are aromatic. Autocondensation of benzylideneacetone (**111**) yields an unstable chloroferrate which may be **113** or **115**, according to whether a Michael addition to **112** or a crotonic condensation to **114** is first involved.[250] Since compound **113** could readily be prepared from 2,6-dimethyl-4-phenylpyrylium and benzaldehyde, the structure of the reaction product should be easily soluble. Another equivocal product is formed from two moles of benzylideneacetone,[50] but a definite structure (**116**) results from chalcone and benzylideneacetone.[50, 250]



By the condensation of ethylideneacetophenone (**109**, R = Ph, R′ = Me) with acetophenone (**110**, R″ = Ph), the first unambiguous synthesis of 2,6-diphenyl-4-methylpyrylium chloroferrate was effected by Schneider and Ross,[49] elucidating the course of reaction in Section II, D, 2, a.

The dehydrogenative condensation of unsaturated ketones with methyl ketones was used for preparing various series of 2,4,6-triarylpyrylium salts not only by Dilthey, but also by Wizinger and co-workers[377] (for combinations of phenyl, *p*-anisyl, and *p*-dimethylaminophenyl substituents), by Amoros-Marin and Carlin[296] (combinations of phenyl and *p*-chlorophenyl), by Le Fèvre and Le Fèvre[61] (for combinations of phenyl and *m*- or *p*-nitrophenyl), and by others.[378]

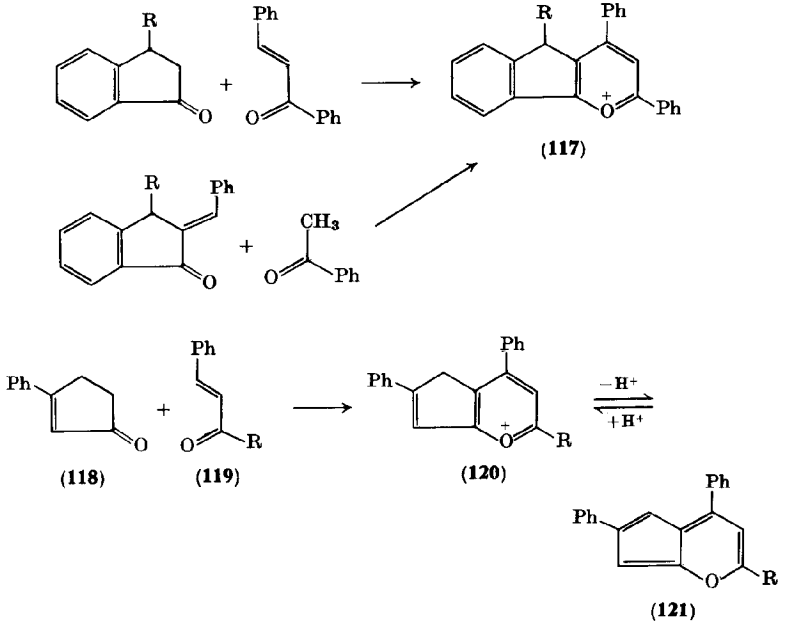
A detailed study of this dehydrogenative condensation in the presence of triphenylmethyl perchlorate or fluoroborate was made by Simalty-Siemiatycki and Fugnitto.[379] The reaction is best carried out in refluxing acetic acid; nitromethane or acetonitrile give less satisfactory results. Chalcone reacts in these conditions with phenylacetaldehyde yielding 2,4-diphenylpyrylium with an unsubstituted α-position. This and similar 2-unsubstituted pyrylium salts prepared by this method are so reactive that they do not afford pyridines on treatment with ammonia in the usual conditions; this behavior is similar to that of the unsubstituted pyrylium perchlorate. The reaction of 1,5-diphenyl-2,4-pentadien-1-one (**63**, R = R″ = Ph, R′ = H) with acetophenone and $Ph_3C^+ClO_4^-$ yields two salts: 2,6-diphenylpyrylium by dehydrogenation of the former reagent alone (cf. Section II, B, 2, e), and 2,6-diphenyl-4-styrylpyrylium by condensation of both reagents.

In the case of t-butyl-substituted α,β-unsaturated ketones, however, no reaction with ketones occurred in the presence of triphenylmethyl fluoroborate;[379a] instead, a 1,2-methyl shift in the unsaturated ketone accompanied by cyclization afforded a crystalline dihydrofurylium salt.[379a,b]

An interesting application with a methylene ketone was described by Boyd[380] for the synthesis of pseudo azulenes from the oxalene[381]

[378] S. A. Kodak, Belgian Patent No. 623,972 (1963); *Chem. Abstr.* **63**, 10102 (1965).
[379] M. Simalty-Siemiatycki and R. Fugnitto, *Bull. Soc. Chim. France* p. 1944 (1965).
[379a] W. Rundel and K. Besserer, *Tetrahedron Letters* p. 4333 (1968).
[379b] K. Dimroth and W. Mach, *Angew. Chem.* **80**, 490 (1968).
[380] G. V. Boyd, *J. Chem. Soc.* p. 55 (1959).
[381] W. Treibs and W. Schroth, *Ann. Chem.* **642**, 82 (1961).

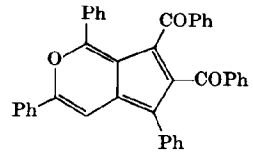
class. Substituted ideno[1.2-*b*] pyrylium salts (**117**, R = H or Ph) may be obtained from indan-1-ones and chalcone, or from benzylideneindan-1-ones and acetophenone, by the action of $FeCl_3 + Ac_2O$. Analogously, 3-phenylcyclopent-2-enone (**118**) reacts with unsaturated ketones (**119**, R = Ph or *t*-Bu) yielding cyclopenta(*b*)-pyrylium chloroferrates (**120**), which may be reversibly deprotonated to colored anhydro bases (**121**).[382, 383]



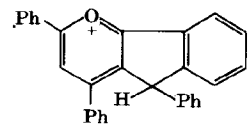
Recently, the cyclopenta[*c*]pyran (**122**) was obtained as a secondary product along with 1,2,3-tribenzoylcyclopropane from phenacyltrimethylammonium hydroxide; a complicated sequence was proposed involving a Michael addition to 1,2-dibenzoylethylene intermediately formed.[384]

An indeno[1.2-*b*]pyrylium (**123**) has been reported to result from the autocondensation of chalcone ($FeCl_3 + Ac_2O$).[385]

[382] G. V. Boyd, *J. Chem. Soc.* p. 1979 (1958).
[383] G. V. Boyd and A. W. Ellis, *J. Chem. Soc.* B, 349 (1966).
[384] J. Harley-Mason and C. R. Harrison, *J. Chem. Soc.* p. 4872 (1963).
[385] G. Oosterloo, Ph.D. Thesis, University of Marburg, 1958.



(122)



(123)

h. *By Dehydrogenative Condensation of Unsaturated Ketones with Aryl Acetylenes.* This reaction is analogous to the previous type in Section II, C, 2, g. Phenylacetylene may replace acetophenone in the condensation with chalcone, in the presence of boron trifluoride etherate.[386] The yield is very low in ether (2%), but is 80% in carbon tetrachloride.

D. Three-Component Syntheses

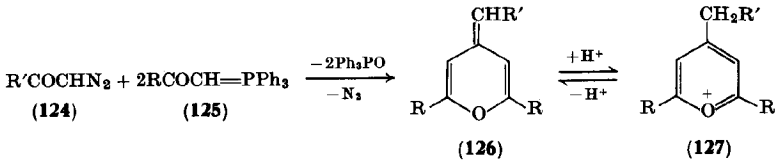
The three possibilities of synthesizing a C_5 chain, namely, $C_2 + C_1 + C_2$, $C_2 + C_2 + C_1$, or $C_1 + C_3 + C_1$, lead to pyrylium salts having identical substituents in positions 2 and 4 in the second case, or 2 and 6 in the first and third cases. Despite this limitation, such syntheses are very convenient because they make the pyrylium salts easily accessible (more so than other six-membered heterocyclic aromatics) from aliphatic starting materials.

1. *From* $C_2 + C_1 + C_2$ *Units*

a. *From Acid Chlorides or Diazoketones and* 2 *Moles of Acylmethylene-Triphenylphosphorane.* Strzelecka, Simalty-Siemiatycki, and Prévost[387] showed that benzoyldiazomethane (**124**, R′ = Ph) reacts at 140° with 2 moles of benzoylmethylene-triphenylphosphorane (**125**, R = Ph) giving a 6% yield of the methylenepyran **126** which may be reversibly protonated to 2,6-diphenyl-4-benzylpyrylium (**127**, R = R′ = Ph).

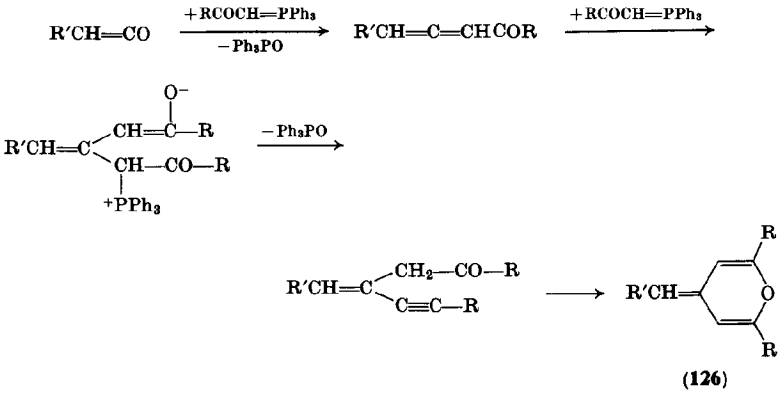
By employing bromophenyl derivatives,[88, 388] the origin of the aryl residues in the reaction product was traced: the 4-aryl residue

[386] W. J. T. Bos and J. F. Arens, *Rec. Trav. Chim.* **82**, 845 (1963).
[387] H. Strzelecka, M. Simalty-Siemiatycki, and C. Prévost, *Compt. Rend.* **254**, 696 (1962).
[388] H. Strzelecka, *Compt. Rend.* **255**, 731 (1962).



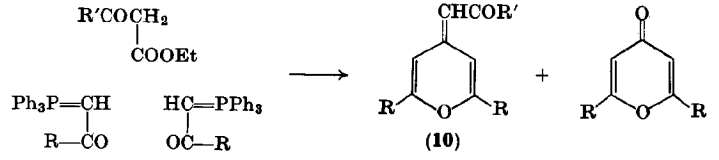
originates from the diazoketone, and the 2- and 6-aryls from the acyl phosphine. The mechanism probably involves a Wolff rearrangement of the diazoketone yielding an aryl ketene (R'CH=CO) which then reacts with the nucleophilic acyl phosphine giving an allenic ketone. A second mole of acylmethylenephosphorane then adds in a Michael-type reaction[389,390] to the activated C=C double bond affording an enolic betaine which eliminates triphenylphosphine oxide, on heating, leaving an acetylenic ketone which then cyclizes to **126.**

Support for this mechanism[391–393] comes from the reaction of diphenylketene with the phosphine **125** leading to **23** (Y = CPh_2), from

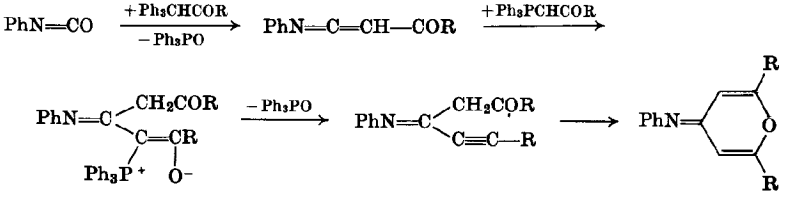


[389] H. J. Bestmann, F. Seng, and H. Schulz, *Chem. Ber.* **96**, 465 (1963); H. Bestmann and F. Seng, *Angew. Chem.* **73**, 154 (1962).
[390] H. J. Bestmann, *Angew. Chem.* **77**, 651 (1965).
[391] C. Prévost, M. Simalty-Siemiatycki, and H. Strzelecka, *Abstr. Papers 19th IUPAC Congr., London* Paper A1–120, p. 87 (1963).
[392] C. Prévost, M. Simalty-Siemiatycki, and H. Strzelecka, *IUPAC Symp. Organo-Phosphorus Comds., Heidelberg*, 1964.
[393] H. Strzelecka, M. Simalty-Siemiatycki, and C. Prévost, *Bull. Soc. Chim. France* p. 8 (1964).

the reaction of dibenzoylallene with acylmethylenephosphines (**125**) described under Section II,C,2,f, and from the fact that aroyldiazomethanes can be replaced (with better yields) by arylacetic acid chlorides, which can also yield ketenes by dehydrochlorination (a third mole of acylmethylene-phosphorane is necessary in this case to take up hydrogen chloride, yielding $RCOCH_2PPh_3^+Cl^-$[248]). Phenylacetic anhydride reacts similarly. Interestingly, β-keto esters like ethylbenzoyl acetate are also able to form an α-ketoketene (by splitting off alcohol in refluxing xylene) which reacts with two moles of acylmethylene-phosphorane forming acylmethylene-4*H*-pyrans (**10**). 4-Pyrones are obtained as side products (or possibly intermediates) by condensation with one mole of acylmethylene-phosphorane.[394]



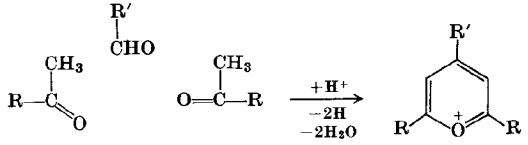
The reaction does not involve dehydrogenation and may also be applied (with low yield) to aliphatic acid chlorides. The reaction with aryl isocyanates proceeds analogously to the reaction with ketenes leading through α-ketoiminoketenes to arylimino-4-pyrones,[395,396] identical to those obtained by Bardone-Gaudemar[236] and described at the end of Section II,B,2,a (see Scheme 6).



SCHEME 6.

[394] H. Strzelecka and M. Simalty-Siemiatycki, *Compt. Rend.* **260**, 3989 (1965).
[395] H. Strzelecka, M. Simalty-Siemiatycki, and C. Prévost, *Compt. Rend.* **258**, 6167 (1964).
[396] M. L. Blanchard, H. Strzelecka, G. J. Martin, M. Simalty, and R. Fugnitto, *Bull. Soc. Chim. France* p. 2677 (1967).

b. *By Dehydrogenative Condensation of Aromatic Aldehydes with 2 Moles of Methyl Ketone.* The title reaction in acetic anhydride in the presence of $FeCl_3$ was described by Dilthey.[46] The formation of chalcones from aromatic aldehydes and aryl methyl ketones can take place in acid medium (e.g., under the action of boron fluoride[267, 397]); therefore, the subsequent reaction of chalcones with aryl methyl ketones can occur in one step. Thus, the sequence is probably D,1,b → C,2,g → B,2,f.

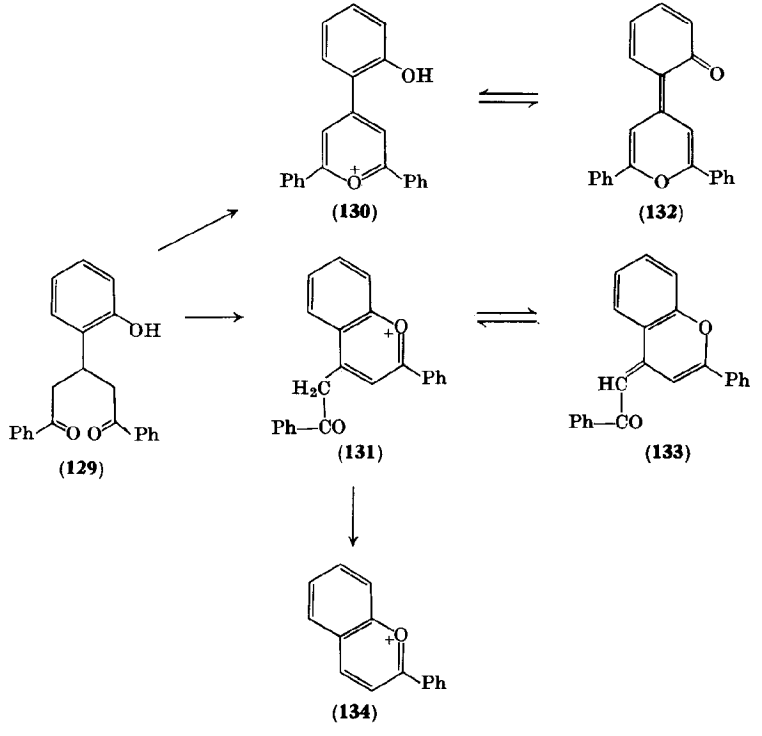


(128)

In comparing his three main syntheses of pyrylium salts (see Sections II,B,2,f; C,2,g; and D,1,b) besides his less general syntheses (see Sections II,B,2,e; C,2,a; and D,2,a), Dilthey[166] stated that the type in Section D,1,b is the most convenient. This is the standard method for preparing 2,4,6-triarylpyrylium salts with identical 2- and 6-substituents, in particular 2,4,6-triphenylpyrylium.[17, 398, 399] Average yields are 30%; in the presence of $BF_3 \cdot Et_2O$ they can be raised to 40%.[267, 278] The reaction can be applied to substituted acetophenones and benzaldehydes, with *p*-anisyl, tolyl, halophenyl, or dimethylaminophenyl substituents,[267, 377] with *m*- or *p*-nitrophenyl,[60, 61] or with thienyl groups.[267] Sulfuric acid or phosphorus oxychloride may be employed instead of $Ac_2O + FeCl_3$, possibly with selenium powder to assist in the dehydrogenation.[377] In the presence of 72% perchloric acid[376] (one mole for a mole R'CHO and 2 moles $RCOCH_3$), the yields are 30–50%, and one may advantageously use acetic acid or toluene as solvent.[400–403]

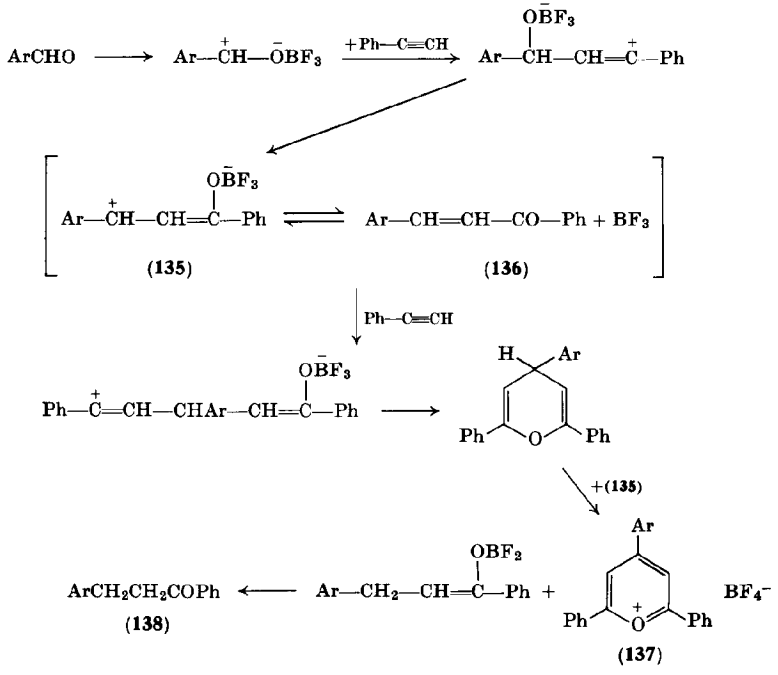
397 D. S. Breslow and C. R. Hauser, *J. Am. Chem. Soc.* **62**, 2385 (1940).
398 H. Kanai, M. Umehara, H. Kitano, and K. Fukui, *Nippon Kagaku Zasshi* **84**, 432 (1963).
399 J. Pascual Vila and A. Escala, *Anales Real Soc. Espan. Fis. Quim. (Madrid)* **46B**, 485 (1950).
400 G. N. Dorofeenko and S. V. Krivun, *Zh. Obshch. Khim.* **34**, 105 (1964).
401 G. N. Dorofeenko and S. V. Krivun, *Zh. Obshch. Khim.* **32**, 2386 (1962).
402 G. N. Dorofeenko, S. V. Krivun, and V. V. Mezheritski, *Zh. Obshch. Khim.* **35**, 632 (1965).
403 G. N. Dorofeenko and S. V. Krivun, USSR Patent No. 154,289 (1962).

A limitation mentioned by Dilthey[46] consists in the possibility of an alternative ring closure when *o*-hydroxybenzaldehyde is employed. The pyrylium salt **130** can be obtained by acid demethylation of the corresponding *o*-anisylpyrylium salt[285]; its blue anhydro base (violone) **132** is unstable and cannot be isolated because it undergoes spontaneous conversion into a yellow isomer **133**.[404, 405] Hill[289] investigated this reaction more closely and found that *o*-hydroxybenzylidenediacetophenone (**129**) with $Ac_2O + FeCl_3 \cdot 6H_2O$ under the usual conditions yields the phenacylflavylium **131** and the flavylium salts **134**, but at 25° the pyrylium salt (**130**) can be isolated (the hydroxy group is acetylated in these conditions).



404 W. Feuerstein and S. von Kostanecki, *Ber. Deut. Chem. Ges.* **31**, 710 (1898).
405 F. M. Irvine and R. Robinson, *J. Chem. Soc.* p. 2086 (1927).

c. *By Dehydrogenative Condensation of Aromatic Aldehydes with 2 Moles of Aryl Acetylene.* As was mentioned when discussing the type in Section II B, 2, c, phenylacetylene is equivalent to acetophenone, and may replace it in pyrylium syntheses carried out in acid medium, in particular in the type in Section II, D, 1, b. Bos and Arens[386] found that aryl aldehydes react with phenylacetylene in the presence of boron fluoride etherate, giving chalcones (**136**) and 4-aryl-2,6-diphenylpyrylium fluoroborates (**137**).

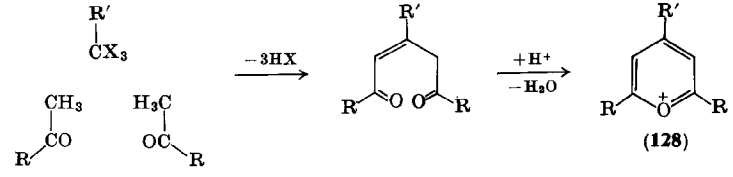


Although the hydrogenated product **138** could not be isolated, its formation is very probable. That chalcones are intermediates in this reaction is made plausible by the reaction described under Section II, C, 2, h.

d. *From 1,1,1-Trihaloalkanes or Ortho Esters and 2 Moles of Methyl(ene) Ketones.* The reaction of a 1,1,1-trihalo- or 1,1,1-trialkoxyalkane with 2 moles of a methyl or methylene ketone to yield a 1,5-pentenedione and hence a pyrylium salt is the rational counterpart

of the synthesis in Section II, D, 1, b. When one wishes to dispense with the dehydrogenation step in the latter reaction, one has to replace the aldehyde by "higher oxidation state" derivative. Curiously enough, an acid chloride or an acid anhydride leads to a different course of the reaction, apparently because the crotonic condensation of the methyl(ene) ketone proceeds faster than the reaction with the acid (cf. the following Section II, D, 2 a). This behavior of acid chlorides or anhydrides, which is markedly different from that of aldehydes, is the origin of an erroneous structural assignment lasting for several years (1916–1922) and making the early pyrylium literature confusing, as will be discussed in the next section.

On the other hand, 1,1,1-trisubstituted alkanes behave similarly to aldehydes, yielding pyrylium salts (**128**) with identical substituents in positions 2 and 6. Thus, Dorofeenko and co-workers condensed 2 moles of acetophenone with 1 mole of benzotrichloride in the presence of perchloric acid obtaining 2,4,6-triphenylpyrylium perchlorate[402]; with 1 mole of ethyl orthoformate, they obtained 2,6-diphenylpyrylium perchlorate (**57**);[406] from *o*-hydroxyacetophenone, orthoformic ester and perchloric acid, 4-ethoxybenzopyrylium perchlorate was formed.[406a]



2. *From $C_2+C_2+C_1$ Units*

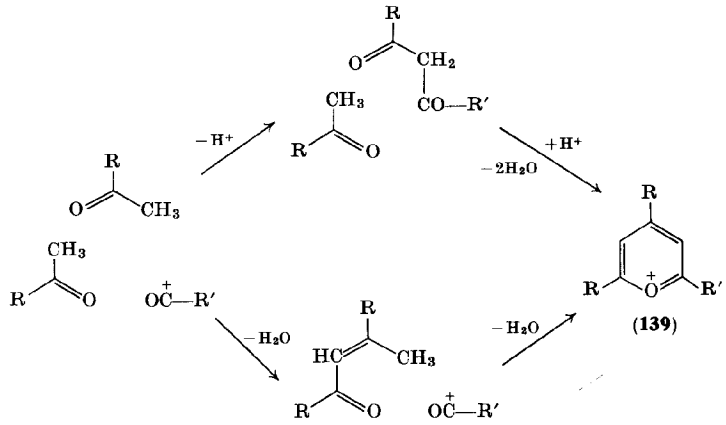
a. *From 1 Mole of Acid Derivative and 2 Moles of Methyl Ketone.* This synthesis was described by Dilthey[46] in 1916; acetophenone with acetic anhydride yields the salt of a nitrogen-free base, which was originally thought to be a benzopyrylium chloroferrate, but afterward, by analogy with the undoubtedly monocyclic triarylpyrylium salts obtained by the method in Section II, D, 1, b, was recognized to be a diphenylmethylpyrylium chloroferrate. However, since the pyridine obtained therefrom by reaction with ammonia was nonidentical with

[406] V. V. Mezheritski and G. N. Dorofeenko, *Zh. Organ. Khim.* **3**, 1533 (1967).
[406a] G. N. Dorofeenko and V. V. Mezheritski, *Zh. Organ. Khim.* **4**, 1305 (1968).

the alleged 2,4-diphenyl-6-methylpyridine prepared by Meyer[407] from 2-methyl-3-cyano-2,6-diphenylpyridine, Dilthey erroneously assigned it the symmetrical structure 2,6-diphenyl-4-methyl-pyrylium. Only 6 years later was this error recognized by Gastaldi[47, 48] (on the basis of the oxidation of the methyl to a carboxy group in the pyridine prepared from the diphenylmethylpyrylium salt), and independently by Schneider and Ross[49] (on the basis of the reaction in Section II,C,1,a). The error in Meyer's work was recognized by Palit and Chatterjea[408] who reinvestigated the structure of Meyer's product and found that by carrying out the hydrolysis and decarboxylation of the cyano group under heating at 290°, 2-methyl-4,6-diphenylpyridine is obtained, identical with the product of Dilthey and Gastaldi. Meyer had used soda lime for decarboxylation, when ring closure to an azafluorene derivative takes place. The real structure, 2,4-diphenyl-6-methylpyrylium, was confirmed by subsequent works of Dilthey and Fischer[50] (who showed that the diphenylmethylpyrylium salt under discussion condenses with benzaldehyde yielding the styrylpyrylium salt **116** whose structure was unequivocally established by a synthesis of the type in Section II,C,2,g), and of Le Fèvre and Pearson[59] (who proved by nitration that a phenyl group is in the γ-position).

The course of the reaction may involve either the acylation of the ketone to a β-diketonic intermediate following thereupon the pathway in Section II,C,2,a, or alternatively the condensation of two moles of ketone to yield an intermediate dypnone which then undergoes acylation following the pathway in Section II,C,1,a. Dilthey and Fischer[69] thought the first alternative more plausible, on the basis of reaction yields, and this lead them to explore the pathway in Section II,C,2,a. Schneider and Ross[49] and Diels and Alder[304] believed that the second alternative operates. Both views are plausible since acylations of methyl ketones to β-diketones are known to take place in the conditions of this reaction,[99, 409] and dypnone has been isolated from acetophenone on treatment with Friedel–Crafts catalysts, in the absence of an acid anhydride or chloride[59, 410, 411] (an excess of catalyst

[407] E. von Meyer, *J. Prakt. Chem.* **78**, 529 (1908).
[408] N. Palit and J. N. Chatterjea, *J. Indian Chem. Soc.* **27**, 667 (1950); *Chem. Abstr.* **46**, 3050 (1952).
[409] C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions* **8**, 59 (1951).
[410] N. O. Calloway and L. D. Green, *J. Am. Chem. Soc.* **59**, 809 (1937).
[411] B. M. Perfetti and R. Levine, *J. Am. Chem. Soc.* **75**, 626 (1953).



prevents the condensation[412]). It is, however, difficult to establish whether one, or the other, or both alternative pathways are involved.

Besides acetophenone,[46, 47, 49, 304, 413–415] this reaction was also applied to *p*-chloro-[416] and *p*-methoxyacetophenone,[46] and even to an aliphatic ketone, acetone (although the yield was stated to be only half as large as that obtained from mesityl oxide, i.e., less than 30%,[304] Dorofeenko and co-workers[417, 418] reported a 45% yield of 2,4,6-trimethylpyrylium perchlorate from acetone, acetic anhydride, and perchloric acid), and is the standard method for preparing pyrylium salts with identical substituents in positions 2 and 4. The acylating agent may be an anhydride[54, 59] in the presence of anhydrous or hydrated ferric chloride, or of boron fluoride,[416] or the acid chloride with ferric chloride.[301] Schneider and co-workers[49, 302, 414, 419–422]

[412] G. Baddeley, *J. Chem. Soc.* p. 232 (1944).
[413] W. Schneider and H. F. W. Meyer, *Ber. Deut. Chem. Ges.* **54**, 1484 (1921).
[414] W. Schneider and F. Seebach, *Ber. Deut. Chem. Ges.* **54**, 2285 (1921).
[415] G. N. Dorofeenko, E. I. Demidenko, and S. V. Krivun, *Izv. Vysshykh Uchebn. Zavedenii Khim. i Khim. Tekhnol.* **19**, 304 (1967).
[416] J. A. Durden and D. G. Crosby, *J. Org. Chem.* **30**, 1684 (1965).
[417] G. N. Dorofeenko and S. V. Krivun, *Ukr. Khim. Zh.* **29**, 1058 (1963); *Chem. Abstr.* **60**, 7977 (1964).
[418] G. N. Dorofeenko, V. I. Dulenko, and N. V. Kovalenko, USSR Patent No. 162,856 (1964); *Chem. Abstr.* **62**, 530 (1965).
[419] W. Schneider and F. Seebach, *Ber. Deut. Chem. Ges.* **54**, 2298 (1921).
[420] W. Schneider and F. Kunan, *Ber. Deut. Chem. Ges.* **54**, 2302 (1921).
[421] W. Schneider and E. Kraft, *Ber. Deut. Chem. Ges.* **55**, 1892 (1922).
[422] W. Schneider and W. Riedel, *Ber. Deut. Chem. Ges.* **74**, 1252 (1941).

employed sulfoacetic acid with acetic anhydride, whereas Diels and Alder[304] recommended the use of 70% perchloric acid, both in conjunction with acetic anhydride. Other anhydrides, namely propionic,[68,300,301,416] butyric, isovaleric,[300,301] isobutyric, hexanoic, heptanoic, phenylacetic, benzoic, and cinnamic[301] anhydrides may replace acetic anhydride.

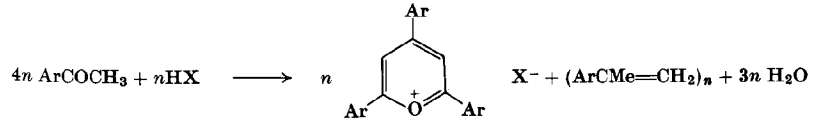
b. *By Acylation of Aromatics (Hydrocarbons or Phenol Ethers).* An interesting development of the reaction in Section II,D,2,a consists in combining the Friedel–Crafts acetylation of an aromatic hydrocarbon or phenol ether to the ketone $RCOCH_3$, with the synthesis of the pyrylium salt **139**. Thus, on acetylating toluene or *o*-xylene with $Ac_2O + HClO_4$, Diels and Alder[304] obtained 2,4-diaryl-6-methylpyrylium salts, whose structure was confirmed by converting the toluene derivative into the known pyridine.[423] Phenol ethers give particularly good yields in this reaction; anisole yields 2,4-di-*p*-anisyl-6-methylpyrylium[424] on treatment with acetic anhydride and sulfoacetic acid,[425,426] zinc chloride,[424] or perchloric acid[417,424,425] (31% yield with the latter catalyst). A similar reaction is given by guaiacol,[421] but not by naphthol ethers in the presence of sulfoacetic acid (α-naphthyl methyl ether yields 4-acetyl-1-naphthol, whereas β-naphthyl methyl ether yields a chromone derivative).[420] Free phenols[413] or benzene[304] failed to yield pyrylium salts on acetylation, but thiophene affords 2-methyl-4,6-di(α-thienyl)pyrylium perchlorate in 41% yield on treatment with $Ac_2O + HClO_4$.[417] Secondary products obtained along with 2,4-diaryl-6-methylpyrylium salts in this reaction, from the aryl methyl ketone intermediately formed, are aromatic acids, dypnones, 2,4,6-triarylbenzenes,[311,419,426–429] and other hydrocarbons or ketones with more complicated structures,[311,430,431] along with 2,4,6-triarylpyrylium salts.

[423] C. Thomae, *Arch. Pharm.* **224**, 653 (1906).
[424] H. Burton and P. F. G. Praill, *J. Chem. Soc.* p. 726 (1951).
[425] H. Burton and P. F. G. Praill, *J. Chem. Soc.* p. 1203 (1950).
[426] T. L. Davis and C. B. Armstrong, *J. Am. Chem. Soc.* **57**, 1583 (1935).
[427] R. E. Lyle, E. J. DeWitt, N. M. Nichols, and W. Cleland, *J. Am. Chem. Soc.* **75**, 5959 (1953).
[428] H. Hopff and A. Heer, *Chimia (Aarau)* **13**, 105 (1959).
[429] H. Hopff, H. R. Schweitzer, A. Ghertsos, A. Heer, and A. Solarski, *Chimia (Aarau)* **12**, 143 (1958).
[430] C. Gastaldi, *Gazz. Chim. Ital.* **51**, II, 289 (1921).
[431] H. W. Moore and H. R. Snyder, *J. Org. Chem.* **28**, 297 (1963).

c. *By Reaction of Aryl Methyl Ketones with Acids.* This formation of 2,4,6-triarylpyrylium salts just mentioned originates in a different reaction which is also related to the type in Section II,D,2,a, and takes place when aryl methyl ketones are treated with strong acids, such as dry hydrogen chloride,[427] sulfuric acid without[432] or with potassium pyrosulfate,[426,428] boron fluoride or its etherate.[267,278,306,376,416,433] The mechanism of the reaction remained obscure for several years because apparently one carbon atom is lost in the reaction. Dovey and Robinson[376] noted that in the formation of 2,4,6-triphenylpyrylium from acetophenone no evolution of methane can be detected. After tentative explanations by Le Fèvre,[432] and Schneider and Keller,[311] the mechanism was finally explained by Elderfield and King,[306] on the basis of the formation of benzoic acid from acetophenone by the action of strong acids, as had been observed as early as 1886,[434] and confirmed later.[435,436] Thus, the reaction consists in the formation of a dypnone which is deacylated in part by the acid:

$$ArCMe{=}CH{-}COAr + H^+ \rightarrow ArCO^+ + ArCMe{=}CH_2$$

(yielding an acyl cation and α-methylstyrene which polymerizes, cf. Ivanov and Ivanov[215] and Bergmann *et al.*[437]), while the remaining dypnone reacts with the acyl cation forming the 2,4,6-triarylpyrylium salt. The reversibility of the aliphatic acylation (of which the above reaction is an example) was proved by chemical and isotopic labeling techniques, as will be discussed in Section II,D,3,a. The overall reaction may therefore be written as in Scheme 7.



SCHEME 7.

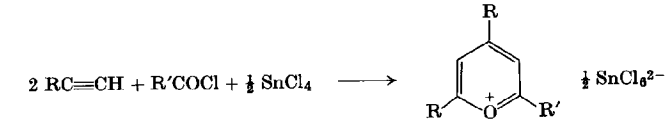
[432] R. J. W. Le Fèvre, *J. Chem. Soc.* p. 1467 (1938).
[433] R. Lombard and J. P. Stephan, *Compt. Rend.* **237**, 333 (1953).
[434] E. Krekeler, *Ber. Deut. Chem. Ges.* **19**, 674, 2623 (1886).
[435] F. Heinrich and A. Wirth, *Monatsh. Chem.* **25**, 442 (1904).
[436] J. H. Simons and E. O. Ramler, *J. Am. Chem. Soc.* **65**, 1390 (1943).
[437] E. Bergmann, H. Taubadel, and H. Weiss, *Ber. Deut. Chem. Ges.* **64**, 1494 (1931).

In the case when boron fluoride or its etherate is employed, the protonic acid is formed according to the following schemes (water is produced in the reaction)[267, 278, 306]

$$2\,BF_3+H_2O \rightarrow HBF_4+F_2BOH$$
$$BF_3+H_2O \rightarrow H[BF_3OH]$$
$$4\,BF_3+3\,H_2O \rightarrow 3\,HBF_4+B(OH)_3$$

Besides acetophenone, this reaction was also applied to *p*-methoxy- and *p*-bromoacetophenone,[428, 429] but in all cases yields are low.

d. *From One Mole of Acid Derivative and Two Moles of Aryl Acetylene.* Taking into account the relationship between pairs of reaction types in Sections II,B,2,a and B,2,c, C,2,g, and C,2,h, or D,1,b and D,1,c, where an aryl methyl ketone and an aryl acetylene may replace one another, the pyrylium salt synthesis recently described by Schmidt[365, 438] is a logical consequence of the type in Section D,2,a, by replacing $RCOCH_3$ with RC≡CH. So far the reaction has been applied only to aromatic acid derivatives $R'CO^+$ (R′ = Ph, *o*- or *p*-ClC_6H_4, *p*-MeC_6H_4, but aliphatic groups R′ could probably also be employed) and to phenylacetylene, R = Ph.



(139)

The reaction was carried out in excess of the acid chloride with cooling and gave yields of 55–80%. Of the catalysts tested, stannic chloride gave the best results.[438]

From the two possible intermediates (a vinylacetylene, or a β-chlorovinyl ketone as in Section II,C,2,c) the latter would appear more probable; the addition of benzoyl chloride to phenylacetylene yielding 3-chloro-3-phenylacrylophenone (β-chlorochalcone) is not reported in the literature, however. Replacing the acetylene by Schiff bases or nitriles, azapyrylium or diazapyrylium can be obtained.[439–441]

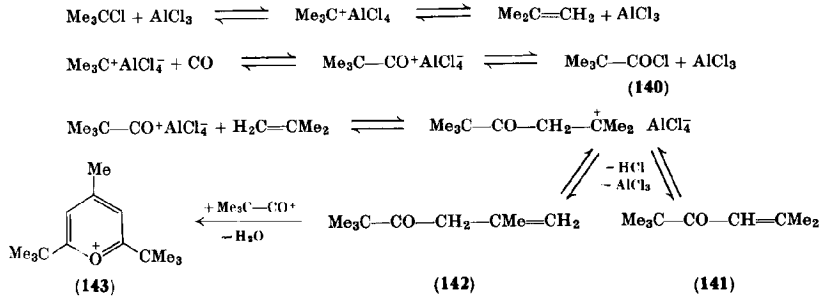
An interesting reaction between Alk-C≡O⁺ and PhC≡CH (leading to $PhCO^+$ which then gives 2,4,6-triphenylpyrylium with PhC≡CH)

[438] R. Schmidt, *Angew. Chem.* **76**, 437 (1964).
[439] R. R. Schmidt, *Tetrahedron Letters* p. 4357 (1965).
[440] R. R. Schmidt, *Angew. Chem.* **77**, 218 (1965).
[441] R. R. Schmidt, *Chem. Ber.* **98**, 3892 (1965); R. R. Schmidt and D. Schwille, *Chem. Ber.* **102**, 269 (1969).

takes place with several alkyl groups (Alk = CCl_3 or $ClCH_2$)[305]; also cf. Meerwein *et al.*[442]

3. *From $C_1+C_3+C_1$ Units*

a. *By Diacylation of Propene Derivatives.*[18] The mechanism of the $AlCl_3$-catalyzed reaction between alkanes[443] or cycloalkanes[444] with carbon monoxide under pressure was demonstrated[443–446] to involve the nucleophilic carbon monoxide and a carbonium ion, and not the formyl cation and an olefin, as had been supposed previously. In support of this idea, *t*-butyl chloride and carbon monoxide under pressure were found to yield, in the presence of aluminum chloride or ferric chloride, pivalyl chloride (**140**) and *t*-butylisobutenyl ketone (2,2,5-trimethyl-4-hexen-3-one) (**141**) and in addition, a 2,6-di-*t*-butyl-4-methylpyrylium salt (**143**).[443] The unexpected formation of the latter product may be accounted for by the following reaction sequence:

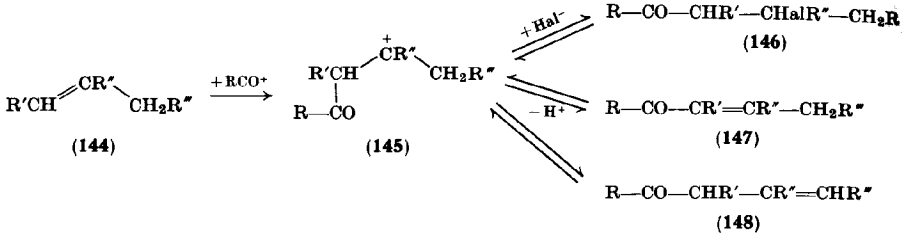


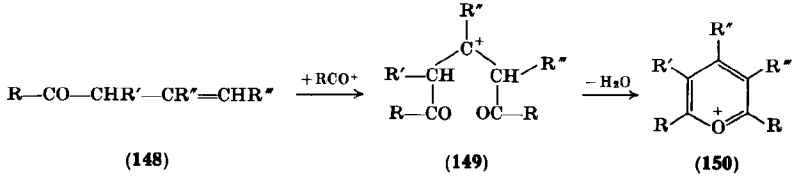
By dehydrohalogenation of *t*-butyl chloride, the nucleophilic isobutene, and by its reaction with carbon monoxide the electrophilic pivalyl chloride, are produced. These two reagents afford the monoacylation products **141** and **142**; the unconjugated enone **142** is able to undergo a second acylation (reaction of the type in Section II,C,1,a) leading to the pyrylium salt **142**.

This was the first clearly recognized diacylation of an olefin. Starting from this observation, Balaban[305, 445] showed that diacylation of

[442] H. Meerwein, P. Laasch, R. Mersch, and J. Spille, *Chem. Ber.* **89**, 209 (1956).
[443] A. T. Balaban and C. D. Nenitzescu, *Ann. Chem.* **625**, 66 (1959).
[444] A. T. Balaban and C. D. Nenitzescu, *Tetrahedron* **10**, 55 (1960).
[445] A. T. Balaban, Ph.D. Thesis, Polytechnical Univ. of Bucharest, 1959.
[446] A. T. Balaban, *Rev. Chim. Acad. Rep. Populaire Roumaine* **7**, 755 (1962).

propene derivatives (**144**) gives pyrylium salts (**150**) in a general reaction, which is one of the best methods available for preparing pyrylium salts with identical substituents in the α-positions, and is a good complement to Dilthey's procedures in Sections II,D,1,b and D,2,a: these latter procedures give best results with aromatic substituents, whereas the diacylation of olefins is to be preferred for aliphatic groups.

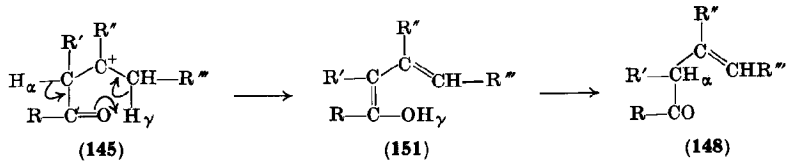




The olefin **144** is acylated to a keto carbonium ion **145** which may either add reversibly a halide anion, yielding a β-halo ketone **146**, or may split off a proton from a β-position relative to the positive charge (other possible reactions of **145**, i.e., 1,2-shifts of a hydride ion or of an alkyl or aryl group; hydride ion addition, substitution of an aryl nucleus or of a second olefinic molecule, and β-fission leading to deacylation or depolymerization, are discussed elsewhere[13]). The yield and purity of the pyrylium salt (**150**) are appreciably higher when starting from the olefin (**144**) than from the equilibrium mixture of unsaturated ketones (**147** $\rightleftharpoons$ **148**). This is explained by the fact that, as Praill and Savillle[447] pointed out, a cyclic transition state favors the elimination of the α-proton from **145** leading to the enol (**151**) which gives the β,γ-enone (**148**). A similar transition state was postulated in the Prins reaction.[448] It is noteworthy that Deno and Chafetz[449]

[447] P. F. G. Praill and B. Saville, *Chem. Ind.* (*London*) p. 495 (1960).
[448] N. C. Yang, D. D. H. Yang, and C. B. Ross, *J. Am. Chem. Soc.* **81**, 133 (1959).
[449] N. C. Deno and H. Chafetz, *J. Am. Chem. Soc.* **74**, 3940 (1952).
[449a] J. K. Groves and N. Jones, *J. Chem. Soc.* C 2215 (1968).

obtained only the β,γ-enone as the primary reaction product in the $ZnCl_2$-catalyzed acetylation of 1-methylcyclohexene, under carefully controlled conditions (cf. **81** in Section II,C,1,a; cf. also ref. 449a).

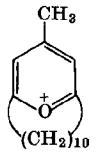


As stated in Section II,C,1,a, Praill and Whitear[322] found that isomesityl oxide (**148**, R = R" = Me, R' = R"' = H) gives a much higher yield of pyrylium salt than the isomeric mesityl oxide. This supports the assumption that **148**, in which the electron density of the double bond is not reduced by conjugation with the carbonyl group like **147**, undergoes the second acylation leading to **149**, whose irreversible dehydration gives **150**. The alternative mechanism, that the enol **151** is acylated,[306, 450] is less probable, although not ruled out.

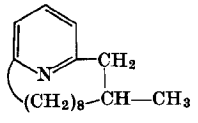
The diacylation of olefins is usually carried out by the Perrier method,[451] i.e., by introducing the olefin into the acylating agent (acid chlorides with catalysts such as $AlCl_3$, $FeCl_3$, $SnCl_4$, $ZnCl_2$, $TiCl_3$, $SbCl_5$,[305] or $HClO_4$,[452] or acid anhydrides with $BF_3 \cdot Et_2O$, $HClO_4$, H_2SO_4, $ZnCl_2$) in solvents such as CS_2, CH_3NO_2, CH_2Cl_2, $(ClCH_2)_2$, or with an excess of the acid derivative as solvent. With aliphatic acids (R = Me, Et, *n*-Pr, iso-Pr, *n*-Bu, iso-Bu, *t*-Bu) yields of 40–60% are obtained,[52, 305, 453] increasing with increasing length of the aliphatic chain. Cyclohexylcarbonyl chloride also gives good yields.[454] With aromatic acids (R = Ph, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, but not with electron-attracting substituents[305, 455]), the yields are lower. Instead of 2 moles of a monocarboxylic acid derivative, one may use 1 mole of

[450] G. Baddeley and M. A. R. Khayat, *Proc. Chem. Soc.* p. 382 (1961).
[451] G. Perrier, *Ber. Deut. Chem. Ges.* **33**, 815 (1900); *Bull. Soc. Chim. France, Ser.* 3 **31**, 859 (1903).
[452] D. Fărcasiu, C. Uncuta, and A. T. Balaban, *Rev. Roumaine Chim.* **12**, 899 (1967).
[453] A. T. Balaban, E. Romas, and C. C. Rentia, *Tetrahedron* **22**, 1 (1966).
[454] A. G. Ismailov and M. R. Atakishieva, *Khim. Geterotsikl. Soedin. Akad. Nauk Latv. SSR* p. 777 (1967); USSR Patent No. 189,443 (1966); *Chem. Abstr.* **67**, 82100 (1967); *Azerb. Khim. Zh.* No. 6, p. 83 (1967).
[455] A. T. Balaban, M. Gavăt, P. T. Frangopol, M. Mocanu, and C. D. Nenitzescu, *Rev. Roumaine Chim.* **9**, 79 (1964).

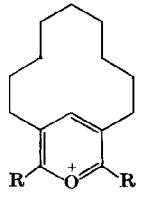
a dicarboxylic acid derivative. By diacylating isobutene with 1,12-dodecanedicarboxylic acid dichloride in ultradilute nitromethane solution, compound **5** was obtained[456]; it afforded a pyridine isomeric with the natural[255] muscopyridine (**152**). The remarkable feature of this reaction is that a bridged aromatic compound is formed in one step from noncyclic starting materials. Attempts to perform a similar cyclic diacylation of propene derivatives with malonyl dichloride to form resorcinols were unsuccessful.[238] Diacylation of cyclododecene afforded the bicyclic pyrylium salt **153**.[456a]



(5)



(152)



(153)

Olefins may be replaced by halides or alcohols which are dehydrohalogenated or dehydrated, respectively, during the reaction; this is advantageous especially with volatile olefins such as isobutene, which can be generated *in situ* from *t*-butyl chloride[305] or *t*-butanol.[52] Dorofeenko and Zhungietu[331, 457] obtained pyrylium salts from alkanes with tertiary carbon atoms, e.g., from cumene, the initial step being a hydride ion transfer from the alkane to the acylium ion. By investigating the reaction of acetic anhydride and perchloric acid with *t*-butanol, Praill independently observed the formation of 2,4,6-trimethylpyrylium perchlorate (**2**).[458, 459] This reaction is the simplest one for preparing **2**, in ca. 60% yield[460]; also cf. Hafner.[310]

Since the rate of aliphatic acylation is higher than that of aromatic acylation, the olefin may possess aromatic substituents; yields are lower, however, than with aliphatic olefins. The types of olefins with aliphatic or aromatic substituents, undergoing diacylation, are shown in Table I.[461] Systematic variation of the structure of the olefin

[456] A. T. Balaban, M. Gavăt, and C. D. Nenitzescu, *Tetrahedron* **18**, 1079 (1962).
[456a] A. T. Balaban, *Tetrahedron Letters* p. 4643 (1968).
[457] G. N. Dorofeenko and G. I. Zhungietu, *Zh. Obshch. Khim.* **34**, 2469 (1964).
[458] P. F. G. Praill, *Chem. Ind. (London)* p. 1123 (1959).
[459] P. F. G. Praill and A. L. Whitear, *Proc. Chem. Soc.* p. 312 (1959).
[460] A. T. Balaban and C. D. Nenitzescu, *Org. Synth.* **44**, 98 (1964).
[461] A. T. Balaban, *Tetrahedron Letters* p. 91 (1963).

showed that propene (**154**) yields 2,6-disubstituted pyrylium hexachloroantimonates.[462] Isobutene (**155**, Alk = Me,[52, 305, 322]), 1-pentene (**158**, Alk = Et),[322], α-methylstyrene (**156**, Ar = Ph),[305, 322] and allylbenzene (**160**, Ar = Ph)[463] are representatives of the four types of monosubstituted propenes (olefins **157** and **158**, etc. written in Table I as equilibrium pairs undergo equilibration during the course of the reaction and yield the same pyrylium salt on diacylation). Disubstituted propenes which gave pyrylium salts on diacylation are 2-pentene (**163**, Alk = Me)[322] and 1,2-diphenylpropene (**164**, Ar = Ph),[305] while 3-ethyl-2-pentene represents a trisubstituted propene of type **173**[322]; 1,2,3-triphenylpropene (**174**, Ar = Ph) could not be diacylated.[305] In the case in which the pyrylium salts did not crystallize, the reaction mixture after diacylation was treated with amomnia for conversion into pyridines: various straight chain 1- or 2-alkenes,[459, 464, 465] and allylbenzene[463] (which partly undergoes acylation at the aromatic nucleus leading to a mixture of two pyrylium salts).

Tetramethylethylene behaves in the $AlCl_3$-catalyzed diacetylation as **155** (Alk = iso-Pr) affording 2,6-dimethyl-4-isopropylpyrylium.[76–78, 305] Although the olefin acylation had been investigated by many chemists beginning with Kondakov[466] (cf. Nenitzescu and Balaban[13] and Balaban and Nenitzescu[18, 305]), the formation of pyrylium salts had escaped notice because they are water-soluble and had been discarded after hydrolysis of the reaction mixture. Only in the study of the $ZnCl_2$-catalyzed acetylation of diisobutene had a crystalline product been observed by Byrns and Doumani[467–469]; its reaction

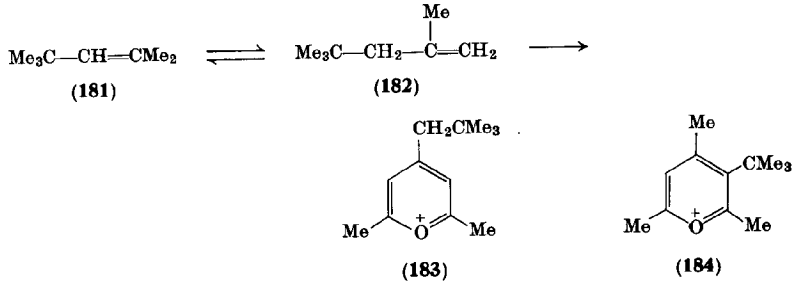
[462] A. T. Balaban, D. Fărcasiu, and C. D. Nenitzescu, *Tetrahedron* **18**, 1075 (1964).
[463] A. T. Balaban, M. Gavăt, G. Mateescu, and C. D. Nenitzescu, *J. Chem. Soc.* p. 2564 (1961).
[464] V. I. Dulenko and G. N. Dorofeenko, *Dopovidi Akad. Nauk Ukr, SSR*, p. 78 (1963).
[465] G. N. Dorofeenko, V. I. Dulenko, and N. V. Kovalenko, *Zh. Obshch. Khim.* **34**, 332 (1964).
[466] I. L. Kondakov, *Zh. Russ. Fiz.-Khim. Obshchestva* **24**, 309 (1892).
[467] A. C. Byrns and T. F. Doumani, *Ind. Eng. Chem.* **35**, 349 (1943).
[468] A. C. Byrns and T. F. Doumani (to Union Oil of California), U.S. Patent No. 2,453,619 (1948); *Chem. Abstr.* **43**, 2634 (1949).
[469] A. C. Byrns (to Union Oil of California) U.S. Patent No. 2,315,046 (1943); *Chem. Abstr.* **37**, 5416 (1943); U.S. Patent No. 2,355,703 (1944); *Chem. Abstr.* **39**, 87 (1945).

TABLE I

TYPES OF OLEFINS UNDERGOING DIACYLATION

Substituents	Possibilities: Total	Possibilities: Non-degenerate	
0	1	1	(154)
1	6	4	(155) (156) (157) (158) (159) (160)
2	12	7	 (161) (162) (163) (164) (165) (166) (167) (168) (169) (170) (171) (172)
3	8	6	(173) (174) (175) (176) (177) (178) (179) (180)

with ammonia gave a nitrogen base. However, they supposed this product to have the structure of a complex between a 1,3-diketone and zinc chloride. Balaban, Ghenea, and Nenitzescu[470] showed in 1961 that the crystalline product is a pyrylium chlorozincate. Nuclear magnetic resonance spectra[471] of the product showed it to have structure **183**. As in the case of tetramethylethylene, only one of the isomeric olefins (**182**) (**155**, Alk = Me_3CCH_2) can be diacylated; from the two possible structures **183** and **184**, only **183** is formed, probably because of steric hindrance in **184**. Two years later, two French patents[472] described the same reaction, quoting Balaban *et al.*[470]; they cover most of the topic described since 1959 by Balaban and co-workers but their structure assignments are wrong, e.g., propene is supposed to yield on diacylation 2,4-disubstituted pyrylium salts.

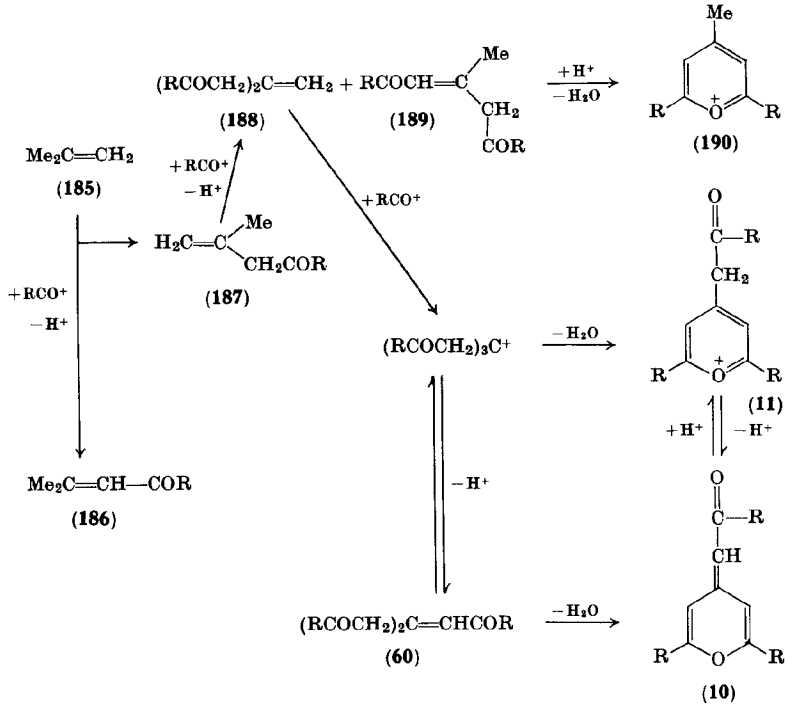


Just as ethylene is able to be monoacylated in the Kondakov reaction to vinyl and β-haloethyl ketones, and propene derivatives can be diacylated to pyrylium salts, isobutene derivatives (**185**) have been shown[249] to undergo triacylation to vinylogous pyrones (**10**). The process may be depicted as involving a sequence of acylations at carbon–carbon double bonds unconjugated with carbonyl groups (**185** → **187** → **188** → **60** → **10**). It is noteworthy that only strong catalysts ($AlCl_3$) are able to bring about triacylation.

[470] A. T. Balaban, A. Ghenea, and C. D. Nenitzescu, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk* p. 1102 (1961).

[471] A. T. Balaban, G. R. Bedford, and A. R. Katritzky, *J. Chem. Soc.* p. 1646 (1964).

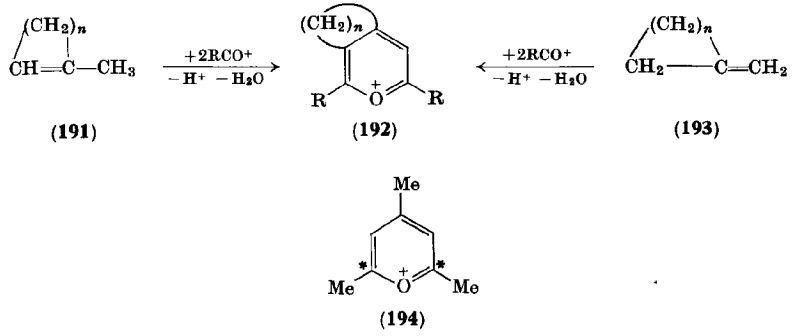
[472] J. Bolle and G. Tomaszewski (to Soc. Anon. Prod. Chim. Shell, Saint-Gobain), French Patent Nos. 1,340,970 and 1,340,971 (1963); *Chem. Abstr.* **60**, 5463 (1964).



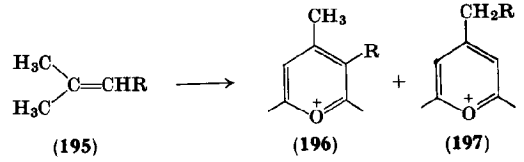
On diacylation of 1-methylcycloalkenes (**191**, $n=3$ or 4), or with higher yields, of methylenecycloalkenes (**193**, $n=3$ or 4), pyrylium salts with fused saturated rings (**192**, $n=3$ or 4, R = Me or Ph) are obtained.[322, 473, 474]

Olefin diacylation with carbonyl-labelled acid derivatives is an excellent method for obtaining ^{14}C-labeled pyrylium salts (**194**) and hence, ring-labeled aromatic compounds such as pyridines and phenols.[475, 476]

[473] A. T. Balaban and C. D. Nenitzescu, *J. Chem. Soc.* p. 356 (1961).
[474] G. N. Dorofeenko, Y. A. Zhdanov, L. N. Yarova, and V. A. Palchkov, *Zh. Organ. Khim.* **3**, 955 (1967).
[475] A. T. Balaban, M. Mărculescu-Frangopol, and P. T. Frangopol, *Isotopes Tech.* **2**, 235 (1962).
[476] A. T. Balaban, M. Frangopol, P. T. Frangopol, and E. Gârd, *Intern. Symp. Prepn. Bio-Med. Appl. Labelled Mol., Venice*, Euratom, Brussels (1964).



An unusual dependence of the structure of the reaction product on the acylating agent (catalyst and acyl group) was observed by Balaban and Nenitzescu in the diacylation of olefins **195**, where R = Me (2-methyl-2-butene[52,477]) or R = Ph (2-methylpropenylbenzene[461]); strong catalysts like $AlCl_3$ or $SbCl_5$ promote the formation of the 2,4,6-trisubstituted compound **197**, whereas weaker



catalysts such as BF_3, H_2SO_4, or $HClO_4$ give mixtures in which **196** prevails, and $BeCl_2$ gives almost only **196**.[478] Baddeley and Khayat[450] as well as Fărcasiu, Fărcasiu, and Balaban[479] reported that in the presence of aluminum chloride, chloro ketone (**200**) forms predominantly the dimethylethylpyrylium salt (**212**), but in the presence of zinc chloride the tetramethylpyrylium salt (**209**); unsaturated ketones (e.g., **204**) are much less sensitive to the nature of the catalyst. The influence of the acyl group can be interpreted, according to Olah and co-workers,[480] by the nature (polarized or ionic) of the complex

[477] A. T. Balaban and C. D. Nenitzescu, *Tetrahedron Letters* No. 2, p. 7 (1960).
[478] A. T. Balaban, A. Barabas, and M. Fărcasiu, *Chem. Ind. (London)* p. 781 (1962).
[479] D. Fărcasiu, M. Fărcasiu, and A. T. Balaban, *Rev. Roumaine Chim.* **9**, 137 (1964).
[480] G. A. Olah, S. J. Kuhn, W. S. Tolgyesi, and E. B. Barker, *J. Am. Chem. Soc.* **84**, 2733 (1962).

between the catalyst and the acid derivative. Tracer experiments evidenced that neither triacylation nor rearrangements are involved in this process[481, 482]; the experimental data can be interpreted (Scheme 8) as implying that, in the presence of strong catalysts, the two olefinic forms **198** and **199**[483] are equilibrating so rapidly that the product **212** is formed from the more reactive isomer **199**, although its equilibrium concentration is very low. In Scheme 8, trimethylethylene is diacetylated in the presence of $AlCl_3$ by pathway **198** $\rightleftharpoons$ **199** $\rightarrow$ **207** $\rightarrow$ **211** $\rightarrow$ **212**, and in the presence of $BeCl_2$ by sequence **198** $\rightarrow$ **201** $\rightarrow$ **205** $\rightarrow$ **210** $\rightarrow$ **209**. Deacylation of chloro ketones is relatively easy,[450, 475, 481] of unsaturated ketones less,[484] and of pyrylium salts impossible.[475, 481] This is confirmed by electrophilic deacylations of acetophenones[434–436] which are very easy when owing to steric hindrance these are nonconjugated (quasi-aliphatic).[485–491] The greater the conjugation energy, the less reversible is the acylation, as proved by tracer experiments.[490]

Mention can be made here of the preparation of 4-pyrones by diacylation of 2-propanones (**213**), which had been studied by Skraup and Priglinger,[492] and by Philippi and Seka[493] for acetone which forms on diacetylation 2,6-dimethylpyrone. More recently, two independent research groups, Letsinger and co-workers[131, 494] and

[481] M. Frangopol, A. Genunche, P. T. Frangopol, and A. T. Balaban, *Tetrahedron* **20**, 1881 (1964).
[482] D. Fărcasiu, A. T. Balaban, and M. Gutman, *Rev. Roumaine Chim.* **9**, 727 (1964).
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[489] G. Nowlin, *J. Am. Chem. Soc.* **72**, 5754 (1950); W. M. Schubert and H. K. Latourette, *J. Am. Chem. Soc.* **74**, 1829 (1952).
[490] M. Frangopol, A. Genunche, N. Negoită, P. T. Frangopol, and A. T. Balaban, *Tetrahedron* **23**, 841 (1967).
[491] A. T. Balaban, *in* "Omagiu pentru Prof. Raluca Ripan," p. 103, Edit. Acad. R. S. Romania, Bucharest, 1966.
[492] H. Skraup and J. Priglinger, *Monatsh. Chem.* **31**, 363 (1910).
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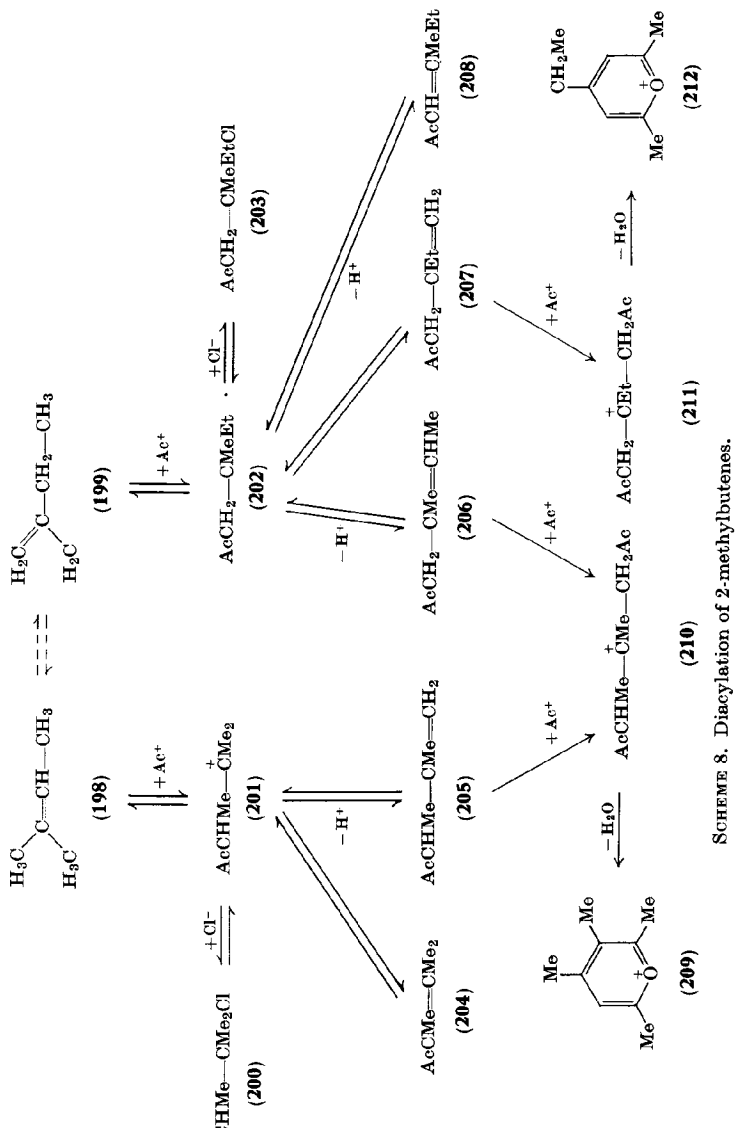
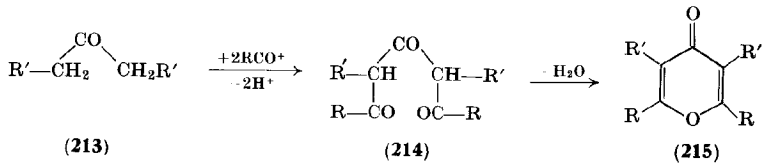
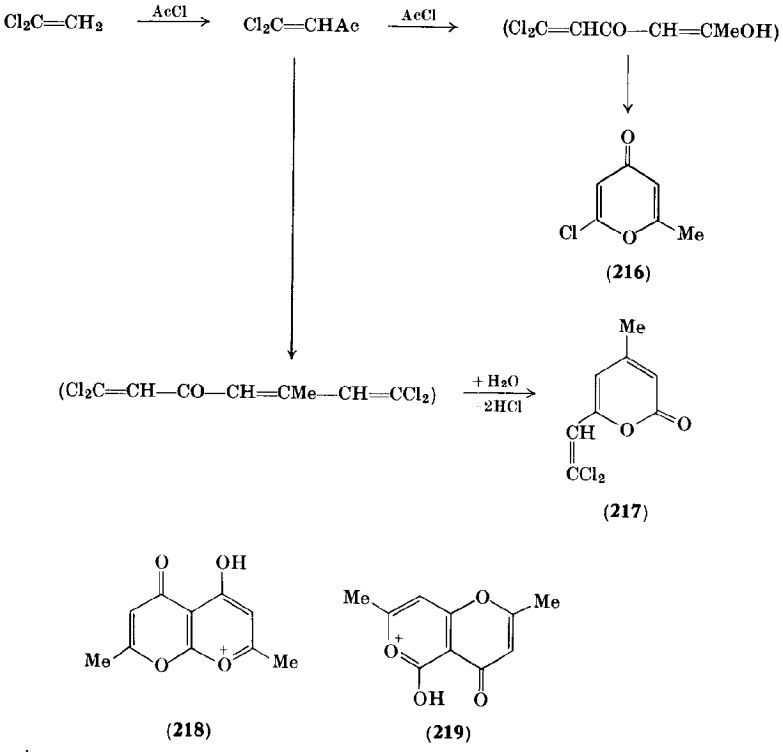


SCHEME 8. Diacylation of 2-methylbutenes.



(213) (214) (215)

Balaban, Mateescu, and Nenitzescu,[495] diacylated 1,3-diphenyl-2-propanone (**213**, R′ = Ph) to 3,5-diphenyl-4-pyrones (**215**), the former with acetic and polyphosphoric acids, the latter with acetyl chloride and aluminum chloride. This reaction follows the usual course of ketone acylation,[13, 235, 236, 409] and has been studied in detail by several research groups in the last 3 years.[102–107] A similar reaction takes



(216) (217) (218) (219)

[495] A. T. Balaban, G. D. Mateescu, and C. D. Nenitzescu, *Rev. Chim. Acad. Rep. Populaire Roumaine* **6**, 295 (1961).

place between acetyl chloride and vinylidene dichloride in the presence of aluminum chloride,[496] when two pyrones with probable structure **216** and **217** are obtained. It should be recalled, however, that 1-phenylpropan-2-ones substituted in positions 3 and 4 of the phenyl group afford isobenzopyrylium salts as outlined in Section II, C, 1, a.[333–337] Praill and Whitear[497] obtained a crystalline perchlorate from acetic anhydride and perchloric acid on standing; it proved to possess structure **218** and to undergo isomerization to **219** under the influence of water. The same products can be obtained on acetylating dehydroacetic acid.

III. Conclusion

The methods described in the present review encompass a wide range of pyrylium salts which have become readily available. In fact, owing to the high electronegativity of the oxygen heteroatom and to the positive charge, the formation of pyrylium salts from acyclic starting materials, as well as the ring-opening reactions of these salts, occurs much more easily than will any other six-membered heterocycles with one heteroatom. Pyrylium salts are useful intermediates in the conversion of aliphatic starting materials into aromatic carbocyclic or heterocyclic compounds.

Though pyrylium salts have had until recently a purely academic interest, some practical applications are beginning to emerge: fluorescent dyes,[498] photosensitizers for silver halides[499–501] or color photo-

[496] O. Wichterle and J. Vogel, *Collection Czech. Chem. Commun.* **19**, 1197 (1954); *Chem. Listy* **48**, 1225 (1954).

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[503] Kodak, S. A., Belgian Patent No. 626,528 (April 15, 1963); *Chem. Abstr.* **60**, 8822 (1964).

graphic emulsions,[502] photoconductive coatings,[503] photoluminiscent materials,[504, 505] organic semiconductors,[506–509] lasers[509a,b] and polymerization catalysts for formaldehyde[510] or vinylic monomers.[511, 512] It can be expected that 2,4,6-trimethyl- and triphenylpyrylium, as well as 2- (or 4-)methyl-4,6-(or 2,6-)diphenylpyrylium perchlorates and/or fluoroborates will soon become commercially available.

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Advances in HETEROCYCLIC CHEMISTRY

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Preface

The tenth volume of this serial publication comprises six chapters, four of which deal with the general chemistry of a specific group of heterocyclic compounds: pyridopyrimidines (W. J. Irwin and D. G. Wibberley), benzofuroxans (A. J. Boulton and P. B. Ghosh), isoindoles (J. D. White and M. E. Mann), and pyrylium salts (A. T. Balaban, W. Schroth, and G. Fischer). The remaining chapters are concerned with indole Grignard reagents (R. A. Heacock and S. Kašpárek) and with cyclic hydroxamic acids (J. B. Bapat, D. St. C. Black, and R. C. Brown).The international flavor of the publication is preserved: our contributors come from six countries in three continents.

We thank the authors and publishers for their cooperation which has allowed production of this volume in less than one year.

Norwich, England
March, 1969

A. R. Katritzky
A. J. Boulton

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